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FOREWORD

IN A STATEMENT introducing the first issue of ENDOCRINOLOGY, in January, 1917, Dr. Lewellys F. Barker wrote as follows:

"This is the first number of a new medical journal, the first to be devoted entirely to the study of the internal secretions. In these days, when the number of medical journals is being rapidly and, it is to be feared, sometimes needlessly increased, it would seem incumbent upon those responsible for the appearance of another journal to give the reasons that, in their opinion, justify its publication."

In the twenty-four years that have intervened the number of medical and biological periodicals has continued to increase and the question of real need which Barker raised has become constantly more serious. In the endocrine field alone at least a half dozen other journals have been established in various countries. With this issue begins another—the first to be devoted solely to the clinical aspects of the subject. It is sponsored by the same society that founded the first periodical in the field.

The development, extension and specialization of knowledge within every broad field brings an urge and often a necessity for the establishment of new journals or the restriction of the scope of existing ones, or both. Seidell has recently pointed out one of the difficulties which make it inexpedient for a given scientific journal to diversify its contents more and more in an attempt to cover a rapidly expanding subject.[1]

"Any one journal contains papers upon a far greater variety of subjects than are of direct interest to an individual or small group of research workers. To obtain the papers concerned with a given problem, a far greater number of reports of no immediate application to that problem will be simultaneously received. These increase the cost of those desired, both for their acquisition and subsequent conservation."

In the past quarter-century the progress in the science and medical application of endocrinology has been truly remarkable, although so much commented upon as to have almost ceased to excite amazement. Experimental discoveries have been applied to medical practice and the clinic, often with gratifying success, but often otherwise. The many new problems raised both in the successful and the unsuccessful applications have in turn fostered further investigation and thus have led to additional discoveries.

With this growth in the subject, its publication needs have likewise grown and become more diversified. ENDOCRINOLOGY was originally published quarterly, then bimonthly, and finally monthly in two large volumes a year. Articles on the strictly clinical aspects and application of the subject have increased proportionately and have come to occupy a large portion of the original journal. They have furthermore changed somewhat in character, becoming, in general, better documented as well as more precise and critical. The gains in precision have perhaps been made possible, or at least have been accompanied, by more specific and pertinent procedures and more detailed data, and by a considerable narrowing of the scope of each subject studied. More and more articles upon increasingly restricted parts of the field have been the rule for the last decade. It is probably safe to predict that these trends will continue for some time to come. Clinical endocrinology is by way of becoming one of the more exact branches of medicine.

THE JOURNAL OF CLINICAL ENDOCRINOLOGY has accordingly been initiated by the Association for the Study of Internal Secretions in order to better serve the growing and more specialized needs of medical practice in this field. It is intended to complement but not to compete with the Association's older journal, ENDOCRINOLOGY. The policies of each journal will be kept in close harmony with those of the other through the agency of the Publication Board of the Association.

[1] SEIDELL, A.: *Science* 92: 345. 1940.

The content of THE JOURNAL OF CLINICAL ENDOCRINOLOGY will be made up of articles of original clinical research, case studies, review articles of timely interest, and occasional special features, centering on the themes of diagnosis, therapy, assay and methods. A section of abstracts of clinical endocrine literature will be included. There will also be a section devoted to correspondence including comments, inquiries and answers, and minor notes.

The field of endocrinology will be interpreted in a very broad sense but the interpretation of the term "clinical" will be rather strict. Papers dealing with the endocrine aspects of other fields of medicine will come within the scope of the Journal, provided these endocrine aspects are explicit and form the more significant part of the contribution.

THE EDITORIAL COMMITTEE

HYPOTHYROIDISM IN CHILDHOOD

I. THE BASAL METABOLIC RATE, SERUM CHOLESTEROL AND URINARY CREATINE BEFORE TREATMENT[1]

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THYROID DEFICIENCY during childhood often gives rise to physical signs which can be readily recognized. Growth is delayed, the ossification of the epiphyseal cartilages and the eruption of teeth are delayed, the proportions of the upper and lower skeletal segments remain those of a younger child, the nasoorbital configuration fails to mature as in the normal child so that the bridge of the nose remains broad and flat as in the infant. The skin and hair sometimes, but not always, show the changes similar to those of adult myxedema. The lowered metabolism is manifested in mental and physical torpor and a sluggish peripheral circulation, causing pallor of the skin. It is apparent that many of the physical signs upon which the diagnoses of hypothyroidism in childhood depend are due to the retardation or distortion of normal processes of growth and development occurring over a considerable period of time. The occurrence of these signs, or their severity, depends upon the age of the patient when thyroid deficiency develops and the duration and degree of deficiency. If hypothyroidism develops in a late period of childhood when the more mature characteristics of the skeleton already have been attained, structural abnormalities will be absent or of mild degree. If the deficiency is of only short duration, the deviation from normal will not be appreciable. If treatment with thyroid has been administered during the crucial stages of development, all structural abnormalities may be prevented. Likewise, it is theoretically possible that a very mild degree of hypothyroidism might exist throughout childhood without causing characteristic abnormalities of body structure. There is no uniform opinion as to the symptoms of mild or borderline forms of hypothyroidism in childhood, and the diagnosis has often been made without substantial proof. Since hypothyroidism may occur without causing uniform and characteristic structural changes, the diagnosis must depend upon a study of functional changes, such as alterations in the basal metabolism, the body chemistry or the circulation.

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[1] This work was aided from January to July, 1938, by a grant from The John and Mary Markle Foundation and since September, 1938, has been supported by the Commonwealth Fund.

GROUPS OF CASES STUDIED

In this and subsequent papers, the study of functional changes in hypothyroidism is to be reported. To determine their significance, it was necessary to compare children with unmistakable hypothyroidism with normal children, or at least those presenting no evidence of any endocrine disorder. For this reason we have included in the hypothyroid groups only those patients who had characteristic clinical signs and in whom the diagnosis was further confirmed by a striking therapeutic response to thyroid medication. The marked therapeutic effect of thyroid upon the growth and osseous development of a hypothyroid child is illustrated in figure 1, in contrast to the lack of response of another dwarfed child who had no evidence of hypothyroidism. In some of the studies the hypothyroid group has been subdivided somewhat arbitrarily into cretins and juvenile hypothyroids, the distinction being based upon whether the history suggested that the deficiency existed from birth or developed later. We realize that the criteria which we have set up may exclude from the hypothyroid group certain children who may be hypothyroid, but are lacking some of the characteristic physical signs, and other children who present some evidences of hypothyroidism, but fail to grow with thyroid medication, perhaps because a pituitary deficiency also exists. Data obtained on such

atypical cases will be reserved until some future time for a discussion of the clinical diagnostic problems of borderline hypothyroidism.

The groups of normal controls in our studies are composed of children showing normal growth and development, who presented no evidence of any endocrine disorder.

In addition to these two contrasting groups we have made some observations on two other groups of children whose body configuration was abnormal. Although the present studies are concerned with a comparison of hypothyroid and normal children, it seems advisable to record here the observations made on those groups. One group is composed of obese children who had no physical signs of hypothyroidism. The other is composed of "unclassified dwarfs" who presented none of the generally accepted signs of hypothyroidism. In a number of instances intensive thyroid therapy was tried and failed to cause any growthy response, as shown in figure 1. It was not feasible, however, to carry out a prolonged therapeutic test in every case. For the time being, we prefer to consider the etiology of dwarfism in these cases as entirely unknown. Only when improved methods for the diagnosis of thyroid and of pituitary deficiency have been found, can the problems of dwarfism be attacked satisfactorily. Since some endocrinologists have placed great importance upon the occurrence of osseous retardation as an evidence of a delay in maturation in contrast to a simple disturbance of growth, the dwarfs have been subdivided into *Group A*, children having marked retardation in osseous development, and *Group B*, children with approximately normal development.

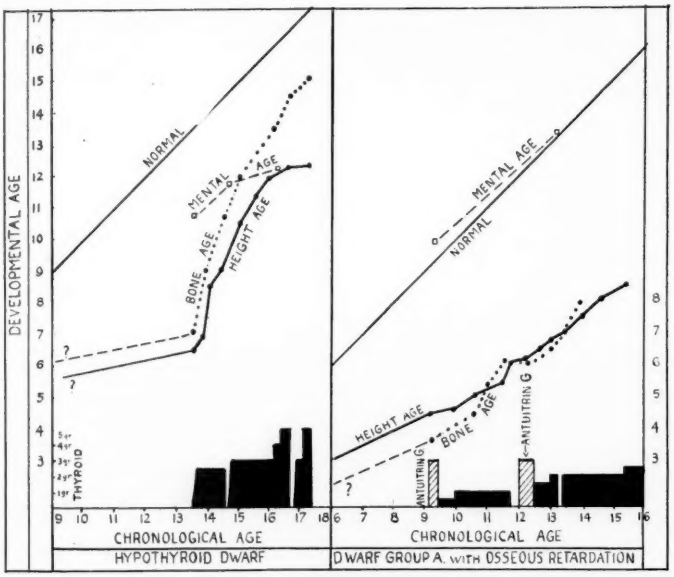

Fig. 1. Growth response in two types of dwarfs.

PROCEDURE AND RESULTS

Basal Metabolic Rate

The determination of the basal metabolic rate is the commonly accepted method of gauging thyroid activity in adults. The method is of questionable value in the diagnosis of hypothyroidism during childhood, partly because of the difficulty of carrying out the measurement and partly because of the difficulty of selecting normal standards from which to calculate the deviation.

Many hypothyroid patients are too young or unintelligent to cooperate in the use of the usual type of respirator. Even when a respiratory chamber is available, it is difficult to attain basal conditions; and the procedure is laborious and not always satisfactory. As Benedict (1) has stressed, the influence of even slight emotional disturbances is often marked and of long duration, and cannot be evaluated readily by the observer. In our own work it was found that certain children who dreaded a routine venepuncture which was often done immediately following a breathing test, consistently had an elevated B.M.R. In measuring B.M.R.'s in a group of children in an institution any disciplinary trouble in one child caused a rise of 10 to 20% in all the members of the group.

Even when the oxygen consumption under basal conditions can be measured properly, there are difficulties in evaluating a deviation from standards which are derived from data on normal children of average body configuration and weight. Hypothryoid children are frequently dwarfed and the calculation of the deviation from normal standards is unreliable in dwarfs and giants as shown by the work of Rowe (2). That the low oxygen consumption of adipose tissue necessarily causes the B.M.R. of obese children to be subnormal, if it is referred to standards based on weight or on surface area, is shown by the work of Topper (3), Talbot (4), Bruch (5) and others. Therefore, in children who differ greatly from the average in weight or build, one is never safe in assuming that a deviation of the B.M.R. from the standard measures thyroid activity exclusively. The selection of the proper standard to use in calculating the deviations of the B.M.R. in abnormal children is open to question. Talbot (4) has made a statistical analysis of the various standards employed, and believes that the one referring the basal caloric requirement to height alone has advantages.

In our experience the measurement of the B.M.R. has not been a satisfactory method for the diagnosis of hypothyroidism. Of 33 children with unquestionable hypothyroidism, a satisfactory determination of the oxygen consumption could be made in only 10. In table 1 these are compared with 7 normal children and 6 obese children. The deviations from the Boothby-Sandiford standard, based on surface area, are compared with the deviations from the Talbot standard based on height.

Most of the hypothyroid children had deviations from the Boothby-Sandiford standards which varied from −19% to −32%. However, two children (*case* 9, 10) consistently had a B.M.R. within the limits commonly accepted as normal. In some of the other patients uniformly low values were not obtained on repeated tests, although the tests were technically satisfactory. The calculation of the deviations from the Talbot height standard showed no special advantages from the standpoint of diagnosis. We were unable to find any close correlation between the degree of the deviation and the severity of the clinical symptoms.

The normal children all fell within the limits of ±10%, whether calculated on the Boothby-Sandiford or the Talbot height standard. The B.M.R.'s of the obese children when calculated on the Boothby-

TABLE 1. BASAL METABOLIC RATES OF HYPOTHYROID, NORMAL AND OBESE CHILDREN

Case	H.L.H. No.	Age	Height	Weight	Cal./24 hr.	Deviation	
						Boothby-Sandiford	Talbot height standard
		yr.	*cm.*	*kg.*			
			Hypothyroid Children				
1	87900	11	130	30	886	−27	−15
2	A-14208	11	120	30	775	−28	−14
3	A-2843	12	110	23	677	−21	−18
4	89454	13	125	32	739	−28	−21
5	A-14184	13	122	30	633	−29	−33
6	47498	14	144	49	943	−32	−22
7	97349	14	130	41	864	−26	−15
8	95193	17	145	42	977	−19	−19
9	58209	18	130	34	1046	− 3	± 0
10	40884	19	142	50	1124	− 7	− 4
			Normal Children				
12	(R) C.H.	7	122	23	993	+ 2	+ 9
13	(R) D.B.	9	132	31	983	− 9	− 2
14	(R) H.E.	9	132	31	1135	+ 5	+10
15	(R) J.H.	10	127	27	1029	+ 3	± 0
16	(R) W.G.	12	152	40	1324	− 1	− 1
17	(R) M.S.	12	147	42	1208	− 2	− 4
18	(R) C.B.	14	145	41	1208	− 5	± 0
			Obese Children				
19	A-13777	10	142	54	1265	−23	+ 3
20	53602	11	147	50	1270	−20	+ 1
21	A-9897	11	139	68	1214	−28	−15
22	A-9192	13	157	115	2016	−15	+42
23	(P) E.L.	14	155	70	1293	−23	− 8
24	93921	10	152	92	1837	−10	+36

Sandiford standard were frequently as low as those of the hypothyroid children. When calculated on the Talbot height standards they were either within normal limits or considerably above it. These children showed no clinical signs of hypothyroidism.

We believe, then, that reliance upon the basal metabolic rate for the diagnosis of hypothyroidism may lead to error in several ways. A normal B.M.R. may occasionally be found in a hypothyroid child, even when the test is apparently technically satisfactory. On the other hand, there is no evidence that a low B.M.R. is indicative of hypothyroidism in an obese child when the calculation is based on standards commonly accepted. The basal caloric requirements of obese children are as great or greater than those of normal children of the same height. It should be mentioned also that we have encountered a number of children of normal build who have low basal metabolic rates, although they present no clinical signs of hypothyroidism. Whether a state of hypometabolism can exist without thyroid deficiency is a disputed question which can be decided only when diagnostic criteria for hypothyroidism have been established.

Serum Cholesterol

Method. The serum cholesterol was determined upon specimens of blood collected before breakfast by the method of Bloor adapted by Pijoan and Walter (6) to the Evelyn photo-electric colorimeter. This method gives a coefficient of error of $\pm 3\%$. The results of workers employing different methods cannot be strictly compared. However, Pijoan and Walter have found that their method does not deviate over 6% from that of Schoenheimer and Sperry.

Results of studies. The values of the fasting cholesterol of 117 children are shown in figure 2. A dot shows the value found in a single determination upon a patient. Two dots connected by a line show the maximum and minimum values found when a number of determinations were made in the same case, indicating the range of spontaneous fluctuations.

a). Normal children. The 57 children of the normal group had concentrations of serum cholesterol varying from 96 mg.% to 308 mg.% with an average of 188 mg.%. In 80% of the patients the cholesterol concentration was between 125 and 225 mg.%, and in only 2 patients was it less than 110 or greater than 280 mg.%. The average for the entire group corresponds very closely to the average for normal children reported by Bronstein (7) as 190 mg.% and by Leopold (8) as 173 mg.%. Approximately one-fifth of the normal children whom we studied had a concentration of cholesterol above the upper limit which other workers found to be about 235 mg.%. Rabinowitch (9) found that the cholesterol varied from 111 to 234 mg.% in 44 normal children under 14 years.

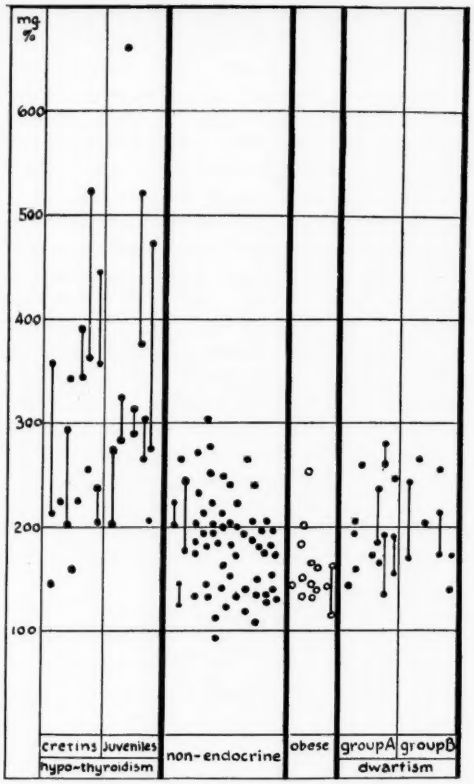

Fig. 2. Serum cholesterol before treatment.

Bronstein (7) found values from 127 to 217 mg.% in 25 children between 2 months and 11 years, while Offenkrantz and Karshan (10) reported concentrations from 137 to 238 mg.% in a similar age group. In adults, however, the upper limit of normal has been reported to be even higher than that which we found, Sperry (11) reporting a normal range from 132 to 392 mg.% and Page (12) 109 to 376 mg.%.

b). Hypothyroid children. In the hypothyroid group we have included only children who had not been treated previously, or had received no thyroid during the year prior to study. In the group of 21 hypothyroid children, the concentration of cholesterol varied from 145 mg.% to 660 mg.%, with an average of 308 mg.%. Among the cretins the concentration varied from 145 to 522 mg.%, with an average of 276 mg.% while in the group of children with the juvenile form of hypothyroidism the range was from 208 to 660 mg.%, with an average of 352 mg.%. It is apparent that in both groups there is a tendency for the cholesterol to be higher than in normal children. Wide fluctuations were found in the concentration of cholesterol of hypothyroid children upon whom repeated determinations were carried out, so that in only 6 of

the 21 children studied were the values consistently above the upper level of 308 mg.% which was found in normal children. Ten of the children had cholesterol levels which never exceeded 308 mg.%.

Hypercholesteremia in adults and children with hypothyroidism has been repeatedly observed. Gildea, Man and Peters (13) in 5 myxedematous adults reported values ranging from 335 to 603 mg.%. Bronstein (7) in a study of 12 hypothyroid children found that in 11 cases the serum cholesterol was between 312 and 782 mg.%, and in one case it was 277 mg.%. However, most of these children had been receiving thyroid previously and the medication had been discontinued for the purpose of the study. We shall point out in a subsequent paper that the withdrawal of thyroid causes the serum cholesterol to increase to higher concentrations than those found before the beginning of treatment. It is important to emphasize that in the present study, which was limited to untreated hypothyroid patients, the cholesterol concentration was frequently within the limits of normal. Mason, Hunt and Hurxthal (14) also found among 23 myxedematous adults that the range of cholesterol was from 217 to 500 mg. However, the serum cholesterol was below 250 mg.% in 4 and below 300 mg.% in 11 of the 23 patients.

c). *Obese children.* The 13 obese children, who were 30 to 130% overweight, had concentrations of serum cholesterol varying from 115 to 253 mg.%, with an average of 164 mg.%, which was slightly lower than that of the normal group. Bruch (5), in a study of 89 obese children, also found the cholesterol value within the normal range with a mean of 200 mg.% and a standard deviation of ± 38.

d). *Unclassified dwarfs.* The 26 dwarfs of unknown etiology all had cholesterol values within the limits of normal, ranging from 138 to 270 mg.%. No difference was found between the dwarfs with retarded bone development (*Group A*), who had an average of 196 mg.%, and those with normal development (*Group B*), who had an average of 204 mg.%.

e). *Fluctuations in serum cholesterol.* In normal children upon whom repeated determinations were made, spontaneous fluctuations in the serum cholesterol were encountered which amounted in some instances to as much as 83 mg.%. Similar fluctuations have been reported in normal adults. Schube (15) studied the whole blood cholesterol of 10 normal adult men over a period of 16 weeks and found that fluctuations amounted at times to as much as 73 mg.%. We found that hypothyroid children who were receiving no treatment showed unexplained fluctuations in the cholesterol concentration of much greater magnitude than the normal children, and, in one case, repeated determinations showed differences in the cholesterol concentrations of as much as 199 mg.%. Fleischmann, Shumacker and Wilkins (16) have found that in thyroidectomized rabbits the concentration of serum cholesterol showed marked fluctuations, amounting to as much as 224 mg.%, whereas in normal rabbits fluctuations were never greater than 34 mg.%.

f). *Influence of age, state of nutrition and diet.* To attempt to explain the constantly low cholesterol values found in some cases of hypothyroidism and the marked fluctuations which occurred in others, the possibility of the influence of age, state of nutrition and diet was considered. Low cholesterol values were found more frequently among the cretins under 2 years of age than among the older hypothyroid children. Although it is possible that age may exert some influence, it cannot be the only factor because a number of the young cretins had high cholesterol levels while some of the older hypothyroid patients had low levels. We have noted no special influence of age upon the cholesterol level of normal children over 2 years, but we have not studied normal infants under this age. Sperry (17) found a range of cholesterol from 71 to 190 mg.% in normal infants from 4 to 25 days of age, and Manicatide (18) reported values from 100 to 180 mg.% in infants from 2 weeks to 14 months. These values are lower than those generally found in children over 2 years of age.

Sex has no apparent influence upon the cholesterol level in children.

We noted no influence of the state of nutrition upon the level of serum cholesterol. This was well shown in the case of a 12-year-old girl with extreme cachexia due to anorexia nervosa. When her weight was 54 lb. (24.7 kg.), or 40% below the average for her height, the cholesterol was 206 mg.%. Nine months later, when her weight had increased to 125 lb. (57 kg.), the cholesterol was 212 mg.%.

No significant relationship of the cholesterol level to the time of feeding was found. In a number of normal children whose serum cholesterol was determined throughout the day, the fluctuations were never greater than 33 mg.% and had no relationship to the time of meals. A number of workers have arrived at the same conclusion. Boyd (19) found that normal individuals ingesting three meals a day showed only very slight variations in the concentration of plasma lipids throughout the day. Turner and Steiner (20) found that the serum cholesterol of an individual tends to remain remarkably constant throughout the day, regardless of the feeding of a breakfast rich in cholesterol. Gardner and Gainsborough (21) found that hypercholesteremia did not occur after a meal, irrespective of the amount of sterol ingested. Barreda (22) did not find a significant increase in blood cholesterol after the ingestion of 5 gm. of cholesterol in 10 cc. of olive oil.

There is no evidence that the low cholesterol val-

ues which were found in some of the hypothyroid children studied, or the marked fluctuations in the cholesterol concentration encountered, were influenced by diet. In a series of 18 children without endocrine disorders, studied at the Children's Hospital School, who were receiving identical diets, there were marked individual differences in the cholesterol levels which varied from 175 to 308 mg.%. On admission to the metabolism ward, where a uniform diet was given some of the hypothyroid patients showed a sudden fall in the cholesterol level, while others showed a rapid rise. Still others had repeated fluctuations on the same diet. Attempts were made in three patients to cause a rise by feeding cholesterol. An untreated cretin of 1 year and a 4-year-old dwarf of *Group B* were each given a daily dose of 4.5 gm. of cholesterol dissolved in olive oil for 7 days. In the case of the cretin, the cholesterol rose from 224 to 249 mg.%, an insignificant change; and in the case of the dwarf the cholesterol dropped from 186 to 162 mg.%. Another cretin was given 3 gm. of cholesterol daily for 3 weeks. In this case thyroid medication had been discontinued 10 weeks previously, and the serum cholesterol had risen to a level of 300 mg.%, and then remained stationary at this concentration for 4 weeks. During the following 3 weeks, when cholesterol was added to the diet, the serum concentration rose from 300 to 358 mg.%. However, when the ingestion of cholesterol was discontinued, the serum level continued to increase during the next 3 weeks to 401 mg.%. The work of Gardner and Gainsborough (21) suggests that prolonged feeding with diets of low or high sterol content may influence the level of serum cholesterol. The change was principally in the cholesterol esters, while the free cholesterol remained practically constant. Turner and Steiner (20) found that a diet high in fat caused a slight rise of serum cholesterol of doubtful significance in 4 out of 9 patients. A diet low in fat did not affect the serum cholesterol.

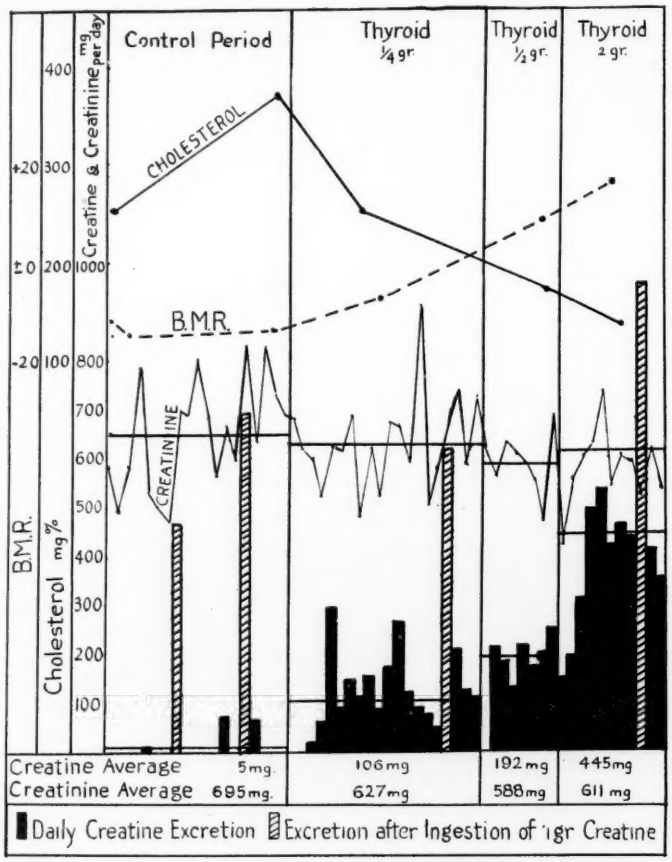

Fig. 3. THE EFFECT OF THYROID ON B.M.R., CHOLESTEROL, CREATINURIA AND CREATINE TOLERANCE.

Creatine Excretion

Patients studied. The creatine excretion was studied in 14 children with hypothyroidism, 9 unclassified dwarfs with marked osseous retardation, 4 unclassified dwarfs without osseous retardation, and 26 children having normal height and development without any evidence of endocrine disturbance. In the latter group there were 18 orthopedic patients at the Children's Hospital School. These patients were selected because they had old, quiescent, orthopedic conditions which presumably would not cause muscular atrophy. However, examination before and after the period of study showed that 9 of these patients, whose extremities were immobilized in casts, had developed muscular atrophy of disuse during the period. In these instances the creatine excretion was abnormally high. These cases, which cannot be considered true normal controls, will be especially designated on the charts. No children suffering from acute febrile conditions were included.

Methods of study. The studies were carried out on a special metabolism ward at Johns Hopkins Hospital or on a special ward set aside for the purpose at the Children's Hospital School. During the studies each child was given a 'low creatine diet,' which contained no meat, fish or meat soups, but included a small amount of creatine in the form of milk, 720 cc. daily. Each child was given a constant diet which provided 2 gm. of protein per kg. of body weight. The total caloric content of the diets varied from 70 to 100 calories per kg., according to the apparent individual needs and appetite. A fairly constant fluid intake was maintained during the period. Some of the children were confined to bed during the entire period; others were ambulatory on the ward under constant supervision. Small infants were kept on metabolism frames for the collection of urine. There was no evidence that creatine excretion was influenced by the amount of activity. Twenty-four-hour specimens of urine were collected and analyzed daily. The specimens of the first 4 days while the children were being adjusted to the diet were discarded. The preformed creatinine and the total creatinine after hydrolysis were determined by the methods of Folin (23). The creatine was expressed as the difference between the preformed creatinine and the total creatinine.

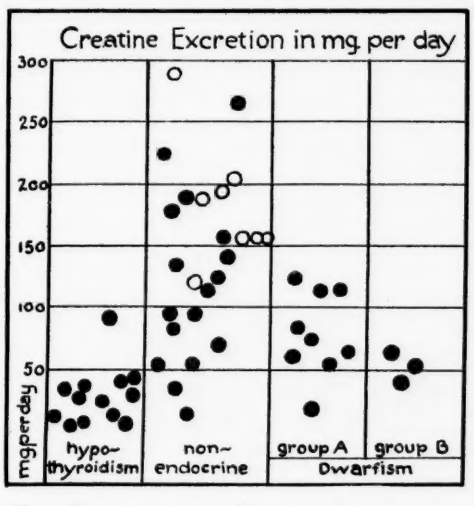

Fig. 4. CREATINE EXCRETION. ● PATIENTS WITHOUT MUSCULAR ATROPHY. ○ PATIENTS WITH MUSCULAR ATROPHY.

Results. In most instances there were marked daily fluctuations in both the creatinine and creatine excretion. The daily fluctuations of creatinine were decidedly greater than those encountered in adults, being frequently as great as 500 mg. These fluctuations apparently were not dependent entirely upon the difficulty of collecting exact 24-hour specimens or upon variations in fluid output. If, however, instead of 24-hour periods, averages representing periods of 7 to 14 days are reported, the level of creatinine excretion is quite constant showing deviations from the average of not over $\pm 15\%$. The level of creatinine excretion was not affected by thyroid medication except in the case of one cretin in whom thyroxin caused a decrease of creatinine excretion with a reversal of the ratio between creatinine and creatine. The great fluctuations encountered in daily creatine excretion are shown in figure 3 and indicate that data based on short periods of study, such as 3 or 4 days, may be misleading and valueless. In the present studies, the values reported represent averages of periods varying from 10 to 14 days.

In figure 4 the creatine excretion of the various groups of patients is expressed in milligrams per day. This shows that the total daily output was lower in the hypothyroid patients than in any others. In comparing children who differ greatly in size, it seemed preferable to express the creatine output as a coefficient of the body weight, as has been done by other workers. In figure 5 the excretions have been charted in terms of the number of milligrams of creatine per kg. of body weight excreted in each 24-hour period.

a). Normal children. Among 17 normal children, the daily excretion, when averaged over a 7 to 14-day period, varied from 0.6 to 7.8 mg./kg./day. The average for the group was 4.2 mg./kg./day. Eight other children, who showed evidence of having undergone some muscular atrophy during the period of study, were not included in these figures. In these cases the average was from 8.0 to 11.8 mg./kg./day. It is possible that in certain children included in the normal group there may have been slight atrophy which was not detected. Therefore, the upper limit for normal is open to question, but if there is an error the value of 7.8 mg./kg./day may be somewhat too high, rather than too low.

b). *Hypothyroid children.* The 14 hypothyroid children excreted from 0 to 3.8 mg./kg. creatine daily, with an average of 1.7 mg./kg./day. No difference was found between young cretins and older hypothyroid children. In only one case, a cretin of 14 months, was there a complete absence of creatinuria over a 21-day period of study.

c). *Unclassified dwarfs.* The 13 unclassified dwarfed children had daily creatine excretions averaging from 0.6 to 6.5 mg./kg., which is within the normal range. There was no difference between *Group A* and *Group B.*

d). *The influence of age and sex.* As shown by figures 4 and 5, there is a tendency for the creatine excretion to be low in hypothyroid children. However, there are great differences in the amount of creatine excreted by normal children and, in many cases, the excretion may be as low as in the hypothyroid cases. It was therefore necessary to analyze the data further, especially in regard to age and sex, which have been reported to have an influence upon the excretion of creatine. In figure 6, the values of creatinuria are shown in relation to age and sex. The various groups of cases are indicated by different symbols. The cases are too few, especially below the age of 4 years and above the age of 10 years, to draw any definite conclusions in regard to the relation of age and sex to creatinuria in normal children, although there is a suggestion of a decreased excretion during the adolescent years. The chart does show, however, that at least after the fourth year no sharp distinction can be made between the hypothyroid cases and normal children, because in each age group there were both hypothyroid and normal children who had the same level of creatinuria.

Our findings disagree somewhat with the opinions expressed by other workers. In the literature there are rather dogmatic statements concerning the creatinuria of normal and hypothyroid children. It is stated that creatinuria is practically absent in premature infants, but is present in full-term newborn infants. It is reported that creatinuria is high in infancy and diminishes gradually during later childhood. Creatinuria is believed to cease about the age of puberty in boys. The continuous creatinuria of girlhood is supposed to merge almost imperceptibly with a periodic creatinuria of the adult female which occurs with the menstrual cycle. Although some workers have found no creatine in the urine of the normal adult male, others have reported its presence. A review of the subject shows that actually very few detailed studies have been made of the level of creatine excretion in normal children. Some of the statements are based upon observations made upon single specimens of urine instead of 24-hour specimens. In other instances studies have been made over periods of only two or three days. Many workers studied the creatine output of children receiving unknown diets in which the amount of creatine ingested was not restricted. The observations of Rose (24) and of Light and Warren (25) which suggest that there is a decrease of creatinuria during adolescence was made upon patients receiving uncontrolled diets.

Marples and Levine (26), Paffrath and Ohm (27), Catherwood and Stearns (28), Rougichitch (29) and Daniels and Hejinian (30) have made careful studies on the creatinuria of infants receiving a low creatine, meat-free diet. Harding and Gaebler (31) made similar studies on 12 children from 2½ years to 9½ years. Shelton and Tager (32) studied 13 normal boys between 7 and 11 years and 18 normal girls between 6 and 13 years, on meat-free diets, but the period of observation was only two days. Table 2 shows the level of creatine reported by various workers in relation to age.

The relationship of creatinuria to the appearance of sex hormones during adolescence is not very well understood. The findings of creatinuria in eunuchs

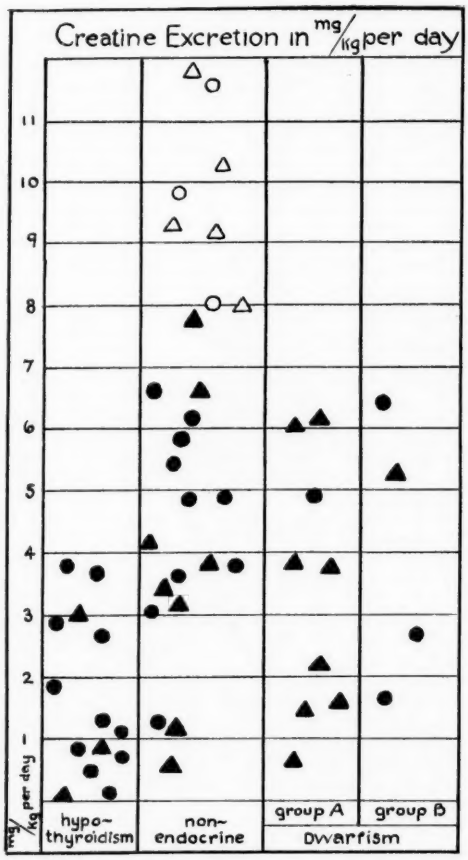

Fig. 5. Creatine excretion. ● girls, ▲ boys, without muscular dystrophy, ○ girls, △ boys, with muscular dystrophy.

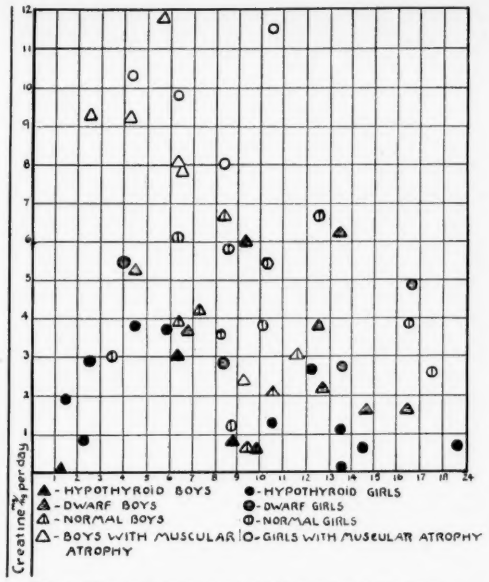
Creatine mg. per day
▲ - HYPOTHYROID BOYS
● - HYPOTHYROID GIRLS
▲ - DWARF BOYS
● - DWARF GIRLS
△ - NORMAL BOYS
○ - NORMAL GIRLS
△ - BOYS WITH MUSCULAR ATROPHY
○ - GIRLS WITH MUSCULAR ATROPHY

Fig. 6. CREATINE EXCRETION IN RELATION TO AGE AND SEX. ABSCISSA, AGE IN YEARS.

(33) and adult men with sexual underdevelopment (34) in contrast to the absence of creatinuria in normal adult men, suggest an influence of the male sex hormone. Kenyon and coworkers (35) found a decrease of creatinuria in 2 of 4 eunuchoids following treatment with testosterone propionate. Animal experimentation has not been able to clarify this point and Pizzolato and Beard (36), on the basis of the literature and their own experiments, come to the conclusion that it is "unjustifiable to attribute a specific function in this connection to any special hormone."

The relationship of creatine excretion to thyroid function was first pointed out by Shaffer (37) in 1908, who found increased creatinuria in Graves' disease. Palmer, Carson and Sloan (38) showed that thyroidectomy abolished creatinuria in this disease. In adult myxedema, Shorr, Richardson and Mansfield (39) found that the administration of thyroid caused the appearance of creatine in the urine, which occurred before any elevation of B.M.R. A few studies have been made on the creatine excretion of hypothyroid children. McCrudden (40) in 1912 found that an 8-year-old cretin excreted 3 mg./kg. of creatine daily, while receiving a meat-free diet. Beumer and Iseke (41) found that a 13-year-old cretin girl excreted no creatine. Poncher, Visscher and Woodward (42) found no creatine in the urine of two cretins 2 years and 5 years of age respectively, and Hess (43) found that creatinuria was absent in two hypothyroid children 6 years and 11 years of age. Langmann and Bruch (44) have recently reported an 8½-year-old cretin who excreted daily 1 mg. of creatine per kg. of body weight, while receiving a meat-free diet.

Creatine Tolerance Test

A number of workers have recorded observations which suggest that the amount of ingested creatine which the body retains varies with the activity of the thyroid. Shorr, Richardson and Wolff (45) introduced the creatine tolerance test. Patients were maintained on a low creatine, meat-free diet, and the amount of endogenous creatine excreted was determined. Creatine (1.32 gm.) was then given at breakfast. During the next 24-hour period, the increase of the creatine excretion above the level of endogenous creatinuria showed the amount of the ingested creatine which was excreted. The remainder of the ingested creatine was believed to be retained in the body or converted into some other substance before excretion. Shorr and his associates (39) reported that a myxedematous adult retained 81%. The administration of thyroid caused more creatine to be excreted, only 33% to 54% being retained. Thorn (46) found a creatine retention in Graves' disease of 58%. He found a creatine retention of 86% to 95% in 7 adults with spontaneous myxedema. After treatment with thyroid there was, however, no change in the creatine retention. Poncher, Visscher and Woodward (42) studied two cretin children but gave 3 gm. of creatine daily

TABLE 2. CREATINE EXCRETION OF DIFFERENT AGE GROUPS REPORTED BY VARIOUS WORKERS

Age	No. of cases	Creatine, mg./kg./day		Observer	Diet	Period of study
		Average	Range			
Prematures	6	Almost none		Marples & Levine (26)	Milk	Part of a day
Prematures	5	Almost none		Paffrath & Ohm (27)	Milk	1 day
1– 8 weeks	41	4.6	Not given	Catherwood & Stearns (28)	Milk	1 day
15–20 weeks	36	10.5	Not given		Milk	1 day
2– 7 months	11	10.3	4.4–18.9	Daniels & Hejinian (30)	Milk	3 days
1½– 7 months	5	11.8	6.0–15.3		Milk	1–5 days
5–12 months	6	17.3	6.8–22.2	Rougichitch (29)	Low creatine	2 days
2½–3½ years	4	8.8	7.5– 9.6	Harding & Gaebler (31)	High protein, low creatine	3 days
4–4½ years	4	5.1	4.2– 5.7	Harding & Gaebler (31)		3 days
9–9½ years	4	4.2	1.0– 6.1	Harding & Gaebler (31)		3 days
5–11 years, (boys)	13	4.9	1.4–11.2	Shelton & Tager (32)	Low creatine	2 days
6–13 years, (girls)	18	7.1	2.4–15.3	Shelton & Tager (32)	Low creatine	2 days

for 5 to 7 days and found a retention of 55% to 81%. Shelton and Tager (32) applied the test to the study of dwarfs and reported an average creatine retention of 62% in 5 dwarfs with marked osseous retardation, compared to 53% in dwarfs with slight osseous retardation and 55% in 13 normal boys. However, these workers determined the level of endogenous creatinuria during a previous control period of only two days.

In our studies of creatinuria in children, we have repeatedly found marked, unexplained fluctuations in the amount of creatine excreted daily. Therefore, in carrying out the creatine tolerance test, we found it necessary to determine the average daily excretion of endogenous creatine during a preceding control period of 7 to 14 days on the low creatine diet. It was also important to maintain a constant level of fluid intake during the studies. The creatine tolerance was determined on 8 children with marked hypothyroidism and 8 children who showed no clinical signs of hypothyroidism. The amount of creatine administered was 1.32 gm. (this is equivalent to 1.00 gm. when calculated as creatinine) in all except two young cretins who were given each 0.66 gm. (equivalent to 0.5 gm.).

The details of creatine tolerance tests which were carried out on a hypothyroid child are illustrated by figure 3. This shows the marked effect of small doses of thyroid upon the creatine excretion, which will be discussed in a subsequent paper. The solid black bars show the daily excretion of creatine on the low creatine diet. The daily creatine excretion was averaged for the control period and each of the periods of treatment. The creatine excreted on the days of the tests is shown by the hatched bars. The tolerance test was performed 4 times, twice during the control period without treatment, once during the period when ¼ grain (16 mg.) of thyroid was given daily, and once after the dose of thyroid had been increased to 2 grains (128 mg.) daily. When the average level of endogenous creatinuria was deducted from the amount of creatine excreted on the day of the test, in the four tests only slight differences in the amount of creatine attributable to the ingestion were found. Retention on the 4 tests was 52.5%, 41.5%, 49.5% and 39.1%.

In table 3 are listed the results of the creatine tolerance test on children with proven hypothyroidism and the control group. The results were very inconsistent. There were marked differences in the amount of creatine retained by the hypothyroid children. The test did not distinguish the hypothyroid children from other patients. The amount of retention was influenced only slightly, if at all, by treatment.

TABLE 3. CREATINE TOLERANCE TESTS

Case	H.L.H. No.	Age & sex, years	Weight	Test dose creatine	Without treatment		With thyroid treatment		
					Av. daily excretion	Retained	Dose of thyroid, daily	Av. daily excretion	Retained
Hypothyroid Group									
			kg.	*gm.*[1]	*mg.*	%	*grains*	*mg.*	%
1	A-9401	1-M	8.5	0.5			*	46	78
2	A-2294	1½-F	8.0	0.5			3	71	55
3	A-3395	1½-M	9.0	0.5			3	52	42
4	A-3914	6-F	12.0	0.5	44	53	3	170	59–71
5	A-2642	9-M	14.0	1.0	18	47–56			
6	87900	12-F	32.0	1.0			3	174	24
7	47498	13-F	48.0	1.0	25	81–90	2	317	73
8	95193	15-F	27.0	1.0	5	52–41	2	369	39
9	58209	17-F	35.0	1.0	20	47–33	2	380	36
Control Group									
10	86323	5-F	17.0	1.0	35	30			
11	73306	-M	22.0	1.0	99	31	2	145	45
12	A-652	9-M	14.0	1.0	133	75	2	153	98
13	63107	9-M	22.0	1.0	95	81			
14	A-5190	9-F	28.0	1.0	33	61			
15	89765	10-M	20.0	1.0	21	40	2	129	34
16	63926	10-M	26.0	1.0	40	69	2	200	53
17	87900	10-F	27.0	1.0	137	34			
18	83008	13-M	24.0	1.0	56	54			
19	A-90	16-M	42.0	1.0	63	84			
20	A-6490	17-F	30.0	1.0	72	44			

[1] 1.32 gm. crystalline creatine equivalent to 1.0 gm. calculated as creatinine.
* Treated with a single dose of 2 mg. of thyroxin.

SUMMARY

The difficulties of determining the basal metabolic rate in children and of interpreting deviations from normal standards are pointed out.

The serum cholesterol of the normal children studied varied from 98 to 308 mg.%. In untreated hypothyroid children, the concentration of cholesterol was frequently above this level. However, in some severe cases of hypothyroidism, the cholesterol was within the normal range. In some hypothyroid children there were marked fluctuations in the cholesterol, amounting at times to as much as 200 mg.%. These fluctuations were much greater than those found in normal children, which did not exceed 83 mg.%. Age, sex, the state of nutrition, the relation to meals, and the fat or sterol content of the diet had little, if any, influence upon the concentration of serum cholesterol.

When averages were calculated for periods of 7 to 14 days, normal children between the ages of 2 years and 17 years excreted from 0.6 to 7.8 mg. of creatine per kilogram of body weight daily, while receiving a meat-free diet providing adequate calories and 2 gm. of protein per kilogram. The creatinuria of hypothyroid children varied from 0 to 3.8 mg. per kilogram. Although there is possibly a tendency for creatinuria to decrease during later childhood and adolescence, the overlapping of the range of creatinuria in the hypothyroid group and the normal group was not accounted for by the age of the patient. In each age group there were both hypothyroid and normal children who had the same degree of creatinuria (table 3).

The measurement of the retention of ingested creatine showed no differences between hypothyroid and normal children. The administration of thyroid to hypothyroid children had no constant effect upon the creatine tolerance.

Although a high cholesterol and a low creatinuria are suggestive of hypothyroidism in the absence of other conditions, the absence of these findings does not exclude hypothyroidism. The creatine tolerance test is of little value in the diagnosis of hypothyroidism during childhood.

In the unclassified dwarfs, the values of cholesteremia and creatinuria which were found, corresponded to the normal group of children rather than the hypothyroid group. No differences were noted between dwarfs with and without osseous retardation.

We wish to thank Dr. Eva Landsberg for her assistance in the creatine studies, and Dr. Hugh Josephs for making cholesterol determinations in conjunction with studies on blood fats, carotene and vitamin A to be reported later. Diets were planned and supervised by Colleen Cox Hambleton of the dietary department of The Johns Hopkins Hospital, for whose help we are grateful.

We wish to express our appreciation to Miss Irene Tabb and the directors of the Children's Hospital School for permission to carry out extensive studies on non-endocrine patients at that institution. Valuable assistance was rendered by Dr. Richard Ferguson and Miss Jean Richardson.

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HYPOTHYROIDISM IN CHILDHOOD

II. SENSITIVITY TO THYROID MEDICATION AS MEASURED BY THE SERUM CHOLESTEROL AND THE CREATINE EXCRETION[1]

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IN THE FIRST PAPER of this series, the writers (1) pointed out the difficulties involved in diagnosing hypothyroidism in the untreated child by a study of the basal metabolic rate, serum cholesterol and creatine excretion. It was shown that the measurement of the basal caloric requirement was often impossible in children, and that, even when it could be measured accurately, the determination of the deviation from the normal was often an unsatisfactory means of diagnosis. Although the concentration of serum cholesterol was high in many untreated hypothyroid children, in some cases it was within the normal range. The amount of creatine excreted by hypothyroid children was usually small, but the output was just as small in many normal children of the same age.

Magnus-Levy (2) first demonstrated that hypothyroid patients show more marked effects from small doses of thyroid than normal individuals. It is generally recognized that doses of desiccated thyroid as small as ½ grain to 2 grains (32 to 128 mg.) daily cause spectacular therapeutic effects in myxedematous adults resulting in disappearance of symptoms, acceleration of the circulation and increase of the basal metabolic rate, whereas similar doses have no apparent effect upon normal individuals. Means and Richardson (3) state that "the effect of the hormone, as would be the case with any catalyst, is greatest when its concentration at the start is lowest." Other hormones, such as those of the parathyroid and the adrenal cortex and insulin, have less effect in normal individuals than in patients or experimental animals in whom there is a specific deficiency. Smith (4) has shown that thyroid extract has a greater effect on the metabolism of the thyroidectomized rat than on that of the normal rat.

It seemed that a study of the physiological responses to standard doses of thyroid or thyroxin might be of value in differentiating between hypothyroid and normal children. Since the determination of the basal metabolic rate of children is frequently unsatisfactory, it seemed advisable to attempt to measure the response to thyroid by means of the decrease in the concentration of serum cholesterol and the increase in the creatine excretion. The work of Luden (5), Mason, Hunt and Hurxthal (6) and others has demonstrated that the administration of thyroid causes a decrease in the serum cholesterol of hypothyroid patients. Shorr, Richardson and Mansfield (7) have shown that in myxedematous adults thyroid causes a marked increase in the creatine excretion. A similar effect in hypothyroid children has been found (8, 9, 10).

The first part of the work was a study of the effect of uniform daily doses of desiccated thyroid given by mouth. During this study, our interest was focused principally upon the excretion of creatine, and observations on the serum cholesterol were not made at frequent intervals in every case. In the later work, the effect of a single dose of thyroxin was studied. At this time we were particularly interested in the effect upon the serum cholesterol, and determinations of the cholesterol were made at frequent intervals.

The methods used for the determination of serum cholesterol and of urinary creatine were described in the previous paper (1). The studies of creatine excretion were all made on children who were kept on a special metabolism ward at the Johns Hopkins Hospital or the Children's Hospital School, and who were given a constant low creatine diet which has been described.

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Sensitivity to Desiccated Thyroid by Mouth

In table 1 are recorded studies of the effect of the oral administration of thyroid, made on 4 groups of children. The first group consisted of 7 hypothyroid children and one myxedematous adult. Only those cases were included in this group in which the diagnosis seemed unmistakable when based on the criteria described in the previous paper (1). In the second group were 11 children who were of average height and weight and who presented no evidence of any endocrine disturbance. A number of orthopedic patients, showing muscular wasting during the period of study, were excluded from this group. The third group was composed of 9 children who had no evidences of hypothyroidism but were abnormal in some respects. In this group there were 4 children, (*cases 25, 26, 27, 28*) whose musculature atrophied from disuse during the study, several malnourished children whose growth was stunted, (*cases 20, 21, 24*), one boy with lipodystrophy (*case 22*) and one with Fröhlich's syndrome (*case 23*). Studies were also made on a fourth group of 4 dwarfs, 3 of whom were classified, as in the previous paper (1), as *Group A*, because of marked retardation of osseous development (*cases 29, 30, 32*)

TABLE 1. EFFECT OF DESICCATED THYROID BY MOUTH

Series No.	Hospital history No.	Age and sex	Creatine excretion								Serum cholesterol							
			Control	¼ gr.	½ gr.	Increase		2 gr.	Increase		Control	¼ gr.	½ gr.	Decrease		2 gr.	Decrease	
			Mg./kg.	Mg./kg.	Mg./kg.	Mg./kg.	%	Mg./kg.	Mg./kg.	%	Mg.%	Mg./kg.	Mg./kg.	Mg.%	%	Mg./kg.	Mg.%	%
Hypothyroid Patients																		
1	A-3395	1-M	0	5.2	3.6	3.6	3600	6.2	6.2	6200	348	180	166	182	52	196	152	44
2	95193	15-F	0.2	3.2	5.7	5.5	2750	12.5	12.3	6250	372	253	173	199	54	131	235	63
3	47498	14-F	0.5	0.8	2.5	2.0	400	8.2	7.7	1540	243	246	165	78	33	123	120	50
4	A-2642	8-M	0.9	6.0	6.1	5.2	577	7.3	6.4	822	300	182		118	39	137	163	54
5	A-2294	1-F	1.8	6.0	9.2	7.4	411	10.4	8.6	477	225	120		105	47	94	131	58
6	87900	13-F	2.6	2.2				12.4	9.8	377	436					237	199	46
7	A-3914	5-F	3.7	6.5	8.8	5.1	138	12.9	9.2	248	272		117	155	57		117+	43+
8	(P) W.H.	56-F	0.4	0.7	0.5	0.1	25	4.0	3.6	900	715		410	305	42	330	385	54
Control Group 1																		
9	A-5190	8-F	1.2	1.1	0.6	0	0	2.5	1.3	108	200	235				231	+	+
10	86323	4-F	3.0	2.7	1.3	0	0	3.7	0.7	23								
11	63107	9-M	3.4	1.9	1.9	0	0	1.7	0	0								
12	(C) 3651	6-M	4.0					10.3	6.3	164	280					203	77	26
13	(C) 3990	16-F	4.4					6.8	2.4	55	252					202	50	20
14	(C) 3801	10-F	5.8	5.2	7.6	1.8	31	11.2	5.4	93	173	191				173	0	0
15	(C) 3475	7-F	6.1	6.1	8.7	2.6	43	12.2	6.1	100	217					231	+	+
16	(C) 3971	11-F	6.6		6.4	0	0	11.8	5.2	80	204					212	+	+
17	(C) 3939	8-M	6.8					11.3	4.5	66	272					197	75	28
18	(C) 3287	6-M	7.7		6.2	0	0	10.8	3.1	40	188					153	35	16
19	(C) 3930	8-F	7.0					11.2	4.2	60	218					193	25	11
Control Group 2																		
20	A-6490	17-F	2.4		2.6	0.2	8	4.7	2.3	96	231					177	54	23
21	63926	12-M	3.1					7.3	4.2	135								
22	A-5559	12-M	3.1					3.8	0.7	22	251					234	17	7
23	73306	7-M	4.3	5.8	5.2	0.9	21	6.3	2.0	46								
24	A-652	8-M	8.8	6.0	8.4	0	0	11.2	2.4	28								
25	(C) 3977	6-M	8.0	4.7	12.3	4.3	54	15.0	7.0	88	250		246			193	57	23
26	(C) 3636	4-M	9.2	8.7	13.1	3.9	42	14.7	5.5	60	203					188	15	7
27	(C) 3891	6-F	9.8		15.2	5.4	55				198					143	50	27
28	(C) 3945	10-F	11.3		11.8	0.5	5				223					212	11	5
Dwarf Group																		
29	A-90	16-M	1.5	0.8	0.8	0	0	1.4	0	0	208		183	25	12	172	36	17
30	83008	13-M	2.2	1.5	1.5	0	0	3.5	1.3	59	270	273				225	45	17
31	66714	8-F	2.7		2.7	0	0	6.7	4.0	148	208					183	25	12
32	75271	13-M	6.2	5.4	9.6	3.4	55	12.0	5.8	93	248					172	76	30
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)

and one of whom (*case 31*) had normal bone development (*Group B*). None had any of the usual clinical signs of hypothyroidism or showed any therapeutic response to thyroid treatment.

In most patients the urinary creatine and creatinine were measured daily during 4 consecutive periods of 7 to 14 days each. The first was a control period during which no treatment was given. In the second period, the child received ¼ grain (16 mg.) of desiccated thyroid daily; in the third period, ½ grain (32 mg.) daily; and, in the fourth period, 2 grains (128 mg.) daily. In a few of the controls, some of these periods were omitted in order to increase the dose of thyroid more abruptly, in the expectation that greater sensitivity to thyroid might be demonstrated in this way. In nearly every case, the level of the serum cholesterol was determined during the control period and at the end of a 2-grain (128 mg.) period. Cholesterol determinations were made during the intermediate periods of thyroid medication in most of the hypothyroid cases, but not in the control cases.

Figure 1 illustrates the manner in which the studies were carried out, showing the observations made upon a hypothyroid boy (*case 4*), a dwarf (*case 30*), and a normal child (*case 9*). In this chart the daily creatine excretion was recorded as the number of milligrams of creatine excreted in each 24-hour period. The hypothyroid boy of 8 years and 9 months was 39 inches (99 cm.) tall, the height of an average 3½-year-old boy. The bones had attained the development of 2 years and there was characteristic epiphyseal dysgenesis. The creatine excretion during the untreated period was low, averaging 18 mg. daily. After the daily administration of ¼ grain (16 mg.) of thyroid was begun, the creatine output increased rapidly to a peak of 224 mg. on the 10th day, but decreased slightly on the 11th and 12th days. During the period of treatment with ½ grain (32 mg.) of thyroid, the creatine output averaged 134 mg., but showed a tendency to decrease slightly. Three days after the thyroid dose was increased to 2 grains (128 mg.), the creatine excretion increased sharply and on the 4th day again reached a peak of 278 mg. Following this, there was again a gradual decrease of creatinuria, although, on the 19th day, the output was still 150 mg., which was more than 8 times the base level. The cholesterol dropped sharply from 255 mg.% to 183 mg. % during the period of treatment with ¼ grain (16 mg.) thyroid and then continued to decrease to 137 mg.% at the end of the 2-grain (128 mg.) period.

The normal child of 8¾ years, who was the twin sister of the hypothyroid boy, had a spontaneous creatinuria averaging 33 mg. per day. The creatine excretion was less than this amount during treatment with ¼ grain (16 mg.) and ½ grain (32 mg.) of thyroid. When the dose of thyroid was increased to 2

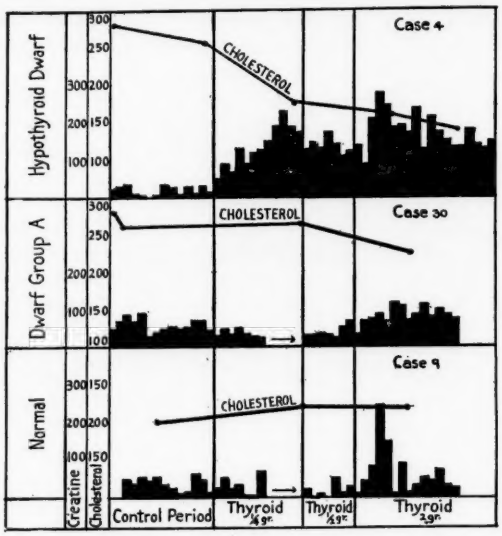

Fig. 1. Responses of 3 groups of children to desiccated thyroid.

grains (128 mg.) there was a marked increase of creatinuria between the third and the seventh days, with a peak of 243 mg. on the fourth day. After the seventh day, the creatine output returned to the base level. Thyroid therapy caused no decrease in the serum cholesterol; in fact, there was a slight increase.

The *Group A* dwarf was a boy of 12 years, 10 months, who had a height age of 6¼ years and a bone age of 6 years. He was active and alert and his cheeks were of ruddy color. Subsequent treatment with thyroid has caused no acceleration of his rate of growth or other clinical change. It is apparent from the chart that the effects of thyroid upon the serum cholesterol and the urinary creatine resembled those of the normal child rather than the hypothyroid child. The spontaneous creatinuria averaged 56 mg. per day. During the periods of treatment with ¼ grain (16 mg.) and ½ grain (32 mg.) of thyroid daily, there was no increase in the creatinuria. When the dose of thyroid was increased to 2 grains (128 mg.) daily, the creatine output increased slightly and was at its height between the 6th and the 10th days. The daily output, however, never exceeded 120 mg. The concentration of serum cholesterol did not decrease during treatment with ¼ grain (16 mg.) of thyroid, but dropped from 270 mg.% to 225 mg.% when 2 grains (128 mg.) were given daily.

In table 1 are recorded the data on all the cases. The average daily excretion of creatine for each period is recorded in terms of milligrams of creatine excreted per kilogram of body weight. In column 7, the increase in the amount of creatine excreted in the ½-

TABLE 2. EFFECT OF DIFFERENT DOSES OF THYROID ON THE CREATINE EXCRETION

Dose of thyroid	Hypothyroid patients					Control patients				
	Cases not showing increase	Cases showing increase		Range of creatinuria	Increase above base level	Cases not showing increase	Cases showing increase		Range of creatinuria	Increase above base level
		No.	%	mg./kg./day	%	No.	No.	%	mg./kg./day	%
Control				0.2– 3.7					1.2–11.8	
¼ grain	2 children 1 adult	5	62.5	0.8[1]– 6.5	60[1]–1600	14	0	0	0.8– 8.7	0
½ grain	1 adult	7	87.5	2.5[1]– 9.8	138[1]–2750	8	6	42.8	0.6–15.2	0–55
2 grains	None	8	100	6.2[1]–12.9	248[1]–6250	5	17	77.3	1.4–15.0	0–164

[1] These figures are exclusive of the adult with myxedema.

grain (32 mg.) period above that of the control period is recorded in mg./kg. and in column 8 in percentage. In column 10 the increased increment of the 2-grain (128 mg.) period over the control period is recorded as mg./kg., and in column 11 as percentage increase. The decrease in the concentration of cholesterol during the 2-grain (128 mg.) period compared to the level of serum cholesterol during the control period is recorded as mg. per 100 cc. of serum in column 18, and as the percentage decrease in column 19.

Table 2 is a summary of the findings in the hypothyroid group compared to those of the control groups. A daily dose of ¼ grain (16 mg.) of thyroid caused an increased creatinuria in 5 out of 8 (62.5%) of the hypothyroid, but in none of the 14 control patients.

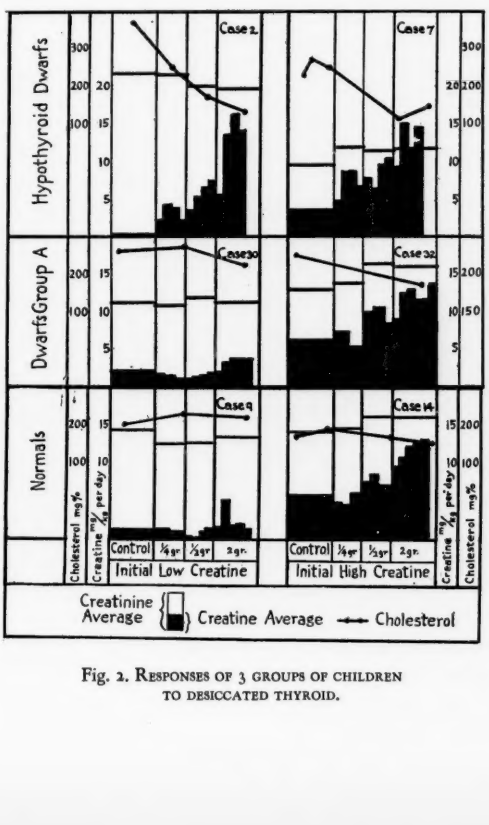

Fig. 2. RESPONSES OF 3 GROUPS OF CHILDREN TO DESICCATED THYROID.

With ½-grain (32 mg.) doses, all 7 hypothyroid children had an increased excretion of creatine but a 56-year-old myxedematous adult did not. This same dose caused an increased creatinuria in 6 out of 14 (42.8%) children who were not hypothyroid. All of the hypothyroid patients (100%) and 17 of the 22 control patients (77.3%) had a creatinuric response to daily doses of 2 grains (128 mg.) of thyroid. With the same doses of thyroid there was no great difference in the range of the level of creatinuria observed in the hypothyroid group compared to the control groups. In fact, normal children receiving thyroid frequently excreted as large, or even larger, amounts of creatine than did the hypothyroid children. However, if one considers that the response to medication is measured by the percentage increase of creatinuria above the base level, marked differences between the hypothyroid children and the controls were apparent. With ½ grain (32 mg.) of thyroid daily, the creatine output of hypothyroid children increased 138 to 2750% above the base level, as compared to an increase of 0 to 55% in the control cases. With 2 grains (128 mg.) of thyroid daily, the increase was 248 to 6250% in the hypothyroid group, compared to 0 to 164% in the control groups.

The hypothyroid children invariably excreted large amounts of creatine during the period of treatment with 2 grains (128 mg.) of thyroid, the daily output amounting to 6.2–12.9 mg./kg. Seven children of the control groups (*cases* 9, 10, 11, 20, 22, 29 and 30) excreted only small amounts of creatine (1.4–4.7 mg./kg. per day) with the same dose of thyroid, whereas the other children of these groups put out amounts varying from 6.7 to 15.0 mg./kg. per day. A study of table 1 shows that the patients of the control group whose creatine excretion was not affected by 2-grain (128 mg.) doses of thyroid, or at the most showed only slight and transient increases, were children who had a low level of spontaneous creatinuria during the initial control periods. The differences in the response to thyroid between children having a low spontaneous creatinuria and those having a high output are illustrated in figure 2. In the left-hand column are

shown the studies on 3 different types of children having a low spontaneous excretion of creatine and in the right-hand column are 3 similar cases having a high spontaneous creatinuria. It is seen that the hypothyroid patients (*cases* 2 and 7) responded to even small doses of thyroid, irrespective of the initial level of creatinuria. The normal child and the dwarf having a low spontaneous creatinuria (*cases* 9 and 30) showed no effect from doses of ¼ grain (16 mg.) and ½ grain (32 mg.) thyroid daily, and a very slightly increased excretion with 2-grain (128 mg.) doses. The normal child and the dwarf having high spontaneous creatinuria (*cases* 14 and 32) showed some effect from ½-grain (32 mg.) doses and put out large amounts of creatine with 2-grain (128 mg.) doses of thyroid.

Table 1 and figures 1 and 2 show that the serum cholesterol decreased markedly with as little as ¼ grain (16 mg.) of thyroid daily in some of the hypothyroid children. With ½ grain (32 mg.) of thyroid daily the decreases varied from 78 to 305 mg.%, a reduction of 33–57% below the control level. When the hypothyroid patients received 2 grains (128 mg.) of thyroid daily, the concentration of serum cholesterol decreased 131 to 385 mg.% below the control level, a reduction of 44–63% below the original value. In the control groups of children, the decrease in the serum cholesterol when 2 grains (128 mg.) of thyroid were given was never greater than 77 mg.% and the reduction never amounted to over 30%, which was within the range of spontaneous fluctuation as reported previously (1). In many instances the drop in the cholesterol concentration was very insignificant, and, in a few cases, an actual increase occurred.

The Effect of a Single Dose of Thyroxin

There are a number of objections to measuring sensitivity by giving small daily doses of desiccated thyroid by mouth. There is a cumulative effect so that the maximum response to a uniform daily dose generally is not reached until the 30th to the 60th day, as shown by Means and Lerman (11). When the dose is increased at intervals shorter than this, there might be irregularities of the effect observed. The study of the effect of daily oral doses is also open to the objection that the patient may gradually acquire an increasing tolerance to thyroid. Because of these difficulties it was decided to study the response to a single large dose of thyroxin.

The effect of a single intravenous dose of 10 mg. thyroxin on the B.M.R. of the myxedematous adult was studied by Boothby and his coworkers (12). The rise in B.M.R. was so constant that Salter, Lerman

TABLE 3. RESPONSE TO SINGLE DOSE OF THYROXIN

Series No.	Harriet Lane history No.	Age and sex	Diagnosis	Dose of thyroxin	Cholesterol Response						Creatine Response					B.M.R.				
					Control	Minimum	Decrease	Maximum effect	Duration of effect	Return to normal	Control	Maximum	Increase	Maximum effect	Return to normal	Control	Maximum	Increase	Maximum effect	Return to base level
				mg.	mg.%	mg.%	mg.%	day	day	day	mg./kg.	mg./kg.	mg./kg.	day	day				day	day
33	A-8696	2½-F	Cretinism	5	349	188	161	13	20	43	2.3	8.0	5.7	8	19					
34	A-8088	6-M	Cretinism or early hypothyroidism	5	284	148	136	17	17	32	3.8	9.4	5.6	4–5	16					
35	A-7353	4½-F	Cretinism	5	358	194	164	18	25	38	3.8	11.9	8.1	4–5	19					
36	A-3924	5½-F	Cretinism	5	300	170	130	9	15	27	6.0	10.3	4.3	3	18					
37	A-9401	1-M	Cretinism	2	244	123	121	11	16	34	1.0	14.7	13.7	16	28					
38	34878	24-F	Cretinism or early hypothyroidism	2	401	207	194	16	27	71	0.7	6.0	5.3	6	14	−28	−10	18		
39	A-14184	13½-F	Juvenile hypothyroidism	2	379	197	182	19	27	36	0.9	6.6	5.7	6	21	−38	−22	16		
40	A-14200	10¾-F	Juvenile hypothyroidism (Excision lingual thyroid)	2	460	390	70	9	10	13	1.1	9.4	8.3	10	24	−46	−35	11		
41	(R) E.M.	16½-F	Cretinism	5	460	231	229	18	32	34	1.1	6.7	5.6	6	20	−46	− 4	42		
			AVERAGE	2	330	145	185	14	24	57										
					356	199	157	14.4	22.5	38.5	2.4	9.2	6.8	7	20					
42	84031	10½-M	Epilepsy	2	234	230	4	5	5	6	1.7	3.4	1.7	2	4					
			Epilepsy	5		194	40	6	6	7		2.7	1.0	4	?					
43	(R) C.B.	14-M	Normal	5	163	143	20	3	3	6						−3	+30	33	6	17
44	(R) W.G.	12-M	Normal	5	96	80	16	3	3	10						+3	+36	33		10
45	(R) J.H.	9-M	Normal	5	140	93	47	3	3	13						+7	+23	16		13
46	(R) C.H.	8-M	Normal	5	155	121	34	3	3	10						+5?	+21	16	6	10
47	(R) M.S.	12-F	Normal	5	190	145	45	6	6	8+						+4?	+36	32	2	9
48	(R) E.H.	14-F	Normal	5	146	124	22	4	7	12						−8	+25	33	4	7
49	(R) H.E.	9-F	Normal	5	187	168	19	6	6	9						+6	+25	19	2	6
			AVERAGE		164	133	31	4½	4½	9										
50	A-7878	6-M	Dwarfism—Group A	2	203	143	60	5	5	12	6.0	10.2	4.2	3	7					
51	96026	4-F	Dwarfism—Group B	2	186	157	29	9	9	20?	6.4	8.8	2.4	4	7					
52	A-9785	4-M	Dwarfism—Group B	2	166	122	44	7	7	10	6.2	12.9	6.7	5	15					
53	A-13763	14-M	Dwarfism—Group A	2	168	224	—	0	0	0	1.8	1.5	—	—	—					
			Dwarfism—Group A	5		135	33	7		10		2.5	0.7	13	16					
54	39480	16-F	Dwarfism—Group A	2	178	135	43	4	0	12	2.9	2.2	—	—	—					
			Dwarfism—Group A	5		126	52	7	0	15		3.7	0.8	10	17					
			AVERAGE		180	150	30	5½		11	4.7	6.0	1.3	7	12					

and Means (13) used this method for the assay of thyroxin and other thyroid constituents. Thompson (14) has made quantitative studies of the difference in sensitivity to thyroid of hypothyroid persons on various levels of metabolism, by injecting 10 mg. of thyroxin and studying the rise in B.M.R. When given at a low level of metabolism (−40%), thyroxin caused an elevation of B.M.R. to −2%, the peak being reached on about the 5th day and the effect lasting over a period of about 80 days. In the same case, when the basal metabolism had assumed a constant level of −4% as a result of thyroid treatment by mouth, the same dose of thyroxin produced a rise to only +16%; the peak was reached on about the 4th day and the effect lasted but 22 days. The total excess heat brought about by thyroxin was about 7 times greater when it was given to a patient in a hypothyroid state than when given at a normal level of metabolism.

In 9 hypothyroid children, (table 3, *cases 33–41*), the serum cholesterol and the creatine excretion were studied, following a single injection of 2 mg. or 5 mg. of thyroxin. As no difference was noted between the intravenous and intramuscular injection of thyroxin, in most cases the drug was given intramuscularly. Satisfactory determinations of the B.M.R. could not be made in most of the hypothyroid cases studied. In one normal child (*case 42*) and 5 dwarfs of *Group A* and *B* (*cases 50–54*), similar studies of the cholesterol and creatine were made. Seven other children of normal height and weight, who had no evidence of any endocrine disorder, were studied as another control group (*cases 43–49*). In the latter group it was impossible to carry out the creatine studies, but the serum cholesterol was determined at frequent intervals and careful measurements of the B.M.R. were made at the same times.

The results of creatine and cholesterol studies are shown in table 3, and in figure 3 the detailed studies on 5 of the hypothyroid patients and 5 control children are shown. Prior to the injection of thyroxin, there were 2 control periods without treatment. The first control period of 7 to 14 days was followed by a period of injections with thyrotropic hormone. (This period is omitted on the chart and the results will be discussed in a subsequent paper.) After the thyrotropic hormone was discontinued and the creatine excretion had returned to the base level, there was a second control period of 3 to 5 days which is recorded on the charts. An injection of 2 mg. or of 5 mg. of thyroxin was then given. Following the injection, the creatine output was determined daily, and the serum cholesterol every third or fourth day, for periods of 40 to 60 days until the cholesterol had returned to the level of the control period. The daily averages of creatine excretion were calculated for 3-day periods and recorded as milligrams per kilogram of body weight.

In the studies of normal children shown in figure 4, only the B.M.R. and the cholesterol were measured. At least two determinations of each were made during a control period before treatment. An injection of 5 mg. of thyroxin was then given. The B.M.R. and serum cholesterol were then determined at intervals of 3 to 5 days until they had returned to the base levels of the control period.

Hypothyroid children. Table 3 shows that the average serum cholesterol of 9 hypothyroid children was 356 mg.% before treatment. After a single dose of thyroxin the average minimum concentration was 199 mg.%, a decrease of 157 mg.%. The decrease in the cholesterol (fig. 3) was usually apparent by the 3rd to the 7th day. The average time at which the minimum concentration was reached was the 14th day. After the 22nd day the cholesterol rose again, reaching the base level on the 38th day. In 4 cases, 33–36, the dose of thyroxin was 5 mg. and, in the other cases 2 mg. With the exception of 3 cases, 36, 38, 40, the magnitude and duration of the cholesterol response was approximately the same in the children receiving 2 mg. as in those receiving 5 mg. of thyroxin. Patient 36 seemed somewhat less sensitive to 5 mg. than most of the children, since the minimum concentration of cholesterol was reached on the 9th day and the effect lasted only 27 days. This may have been due to the fact that this patient was the only one who had received thyroid medication previously. Although treatment had been discontinued 6 weeks prior to the study, its effects probably had not disappeared entirely. Patient 40 also showed less sensitivity to 2 mg. thyroxin than other members of the group. The serum cholesterol decreased only 70 mg.% and the effect lasted only 13 days. However, the creatine output increased from 1.1 mg./kg. to 9.4 mg./kg. Twenty-seven days after the first injection, the experiment was repeated with 5 mg. of thyroxin. With this dose, the cholesterol concentration decreased 229 mg.% and did not return to the former level until after the 34th day. This patient had developed signs of hypothyroidism 5 years prior to the study, following the surgical removal of a lingual thyroid. The relative lack of sensitivity may have been due to the persistence of a small amount of thyroid tissue in some other location. In contrast to these 2 patients showing relatively less sensitivity than the rest of the group is patient 38, a 24-year-old girl with severe signs of cretinism, who had never received treatment. In her case, the injection of 2 mg. of thyroxin caused a decrease in the cholesterol which lasted for 71 days—a much longer effect than generally observed. Omitting the 3 exceptions which have been discussed, the injection of 2 mg. or 5 mg. thyroxin caused a decrease in the serum cholesterol which varied from 121 to 185 mg.% and which lasted from 32 to 57 days.

The effect of thyroxin on the excretion of creatine was more prompt and of shorter duration than on the cholesterol concentration. In 8 cases, the peak of the creatine excretion was reached between the 3rd and

Normal children. In the normal children, the injection of 5 mg. of thyroxin caused a fall in the concentration of serum cholesterol, varying from 16 to 47 mg.%, with an average of 31 mg.%. It is true that

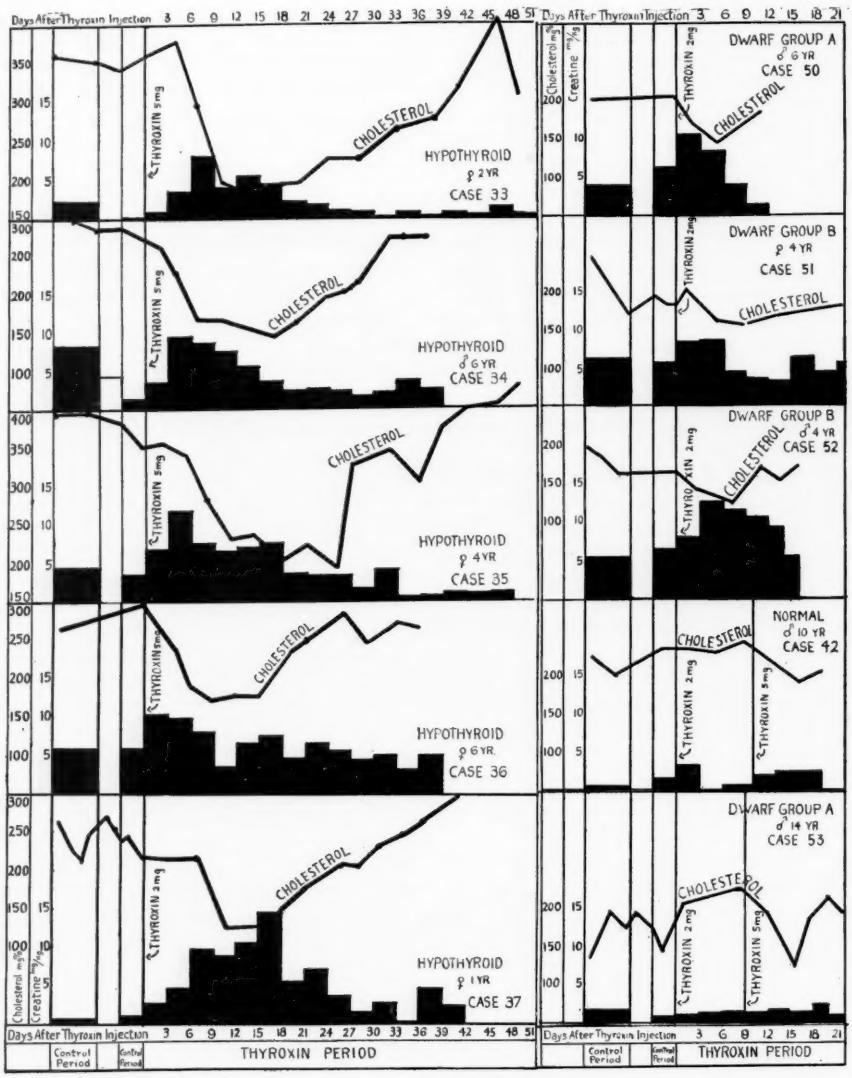
Days After Thyroxin Injection 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51
THYROXIN 5mg
CHOLESTEROL
HYPOTHYROID ♀ 2YR CASE 33
HYPOTHYROID ♂ 6YR CASE 34
HYPOTHYROID ♀ 4YR CASE 35
HYPOTHYROID ♀ 6YR. CASE 36
HYPOTHYROID ♀ 1YR CASE 37
DWARF GROUP A ♂ 6YR CASE 50
DWARF GROUP B ♀ 4YR CASE 51
DWARF GROUP B ♂ 4YR CASE 52
NORMAL ♂ 10 YR CASE 42
DWARF GROUP A ♂ 14 YR CASE 53
THYROXIN 2mg
Cholesterol mg%
Creatine mg/kg
Control Period
THYROXIN PERIOD

Fig. 3. Responses to a single dose of thyroxin.

the 10th day and the excretion had decreased again to the base level by the 14th to the 21st day. In one case, the peak occurred on the 16th day and the level of the control period was reached on the 28th day. The maximum excretion of creatine after treatment was 6.0 to 14.7 mg./kg./day. These values represented increases of 4.3 to 13.7 mg./kg./day above those of the control periods.

the initial concentrations of cholesterol of these patients before treatment were considerably less than those of most of the hypothyroid patients. However, even when this is taken into consideration, the percentage decrease was very much less than in the hypothyroid group. Patient 42, an epileptic boy without any evidence of endocrine disturbance, is of interest in comparison with patient 37, a cretin, because the

original concentrations of cholesterol were approximately the same in the two cases. Each patient received 2 mg. of thyroxin. The serum cholesterol of the cretin decreased from 244 mg.% to 123 mg.%; that of the normal boy from 234 mg.% to 230 mg.%. The normal boy was given an additional 5 mg. of thyroxin 10 days after the first injection and the serum cholesterol decreased to only 194 mg.%.

The effect of thyroxin on the concentration of cholesterol was very transient in the normal children, in marked contrast to the long duration in the hypothyroid children. In the normal group, the concentration of cholesterol reached its lowest point between the 3rd and the 6th day and returned to the base level between the 6th and 13th day.

The creatine excretion was studied in only one of the normal children, *case 42*. In this patient, the injection of 2 mg. and later of 5 mg. of thyroxin caused an insignificant and transient increase in the excretion of creatine.

The determinations of B.M.R. recorded in table 3 and figure 4, were considered satisfactory in 5 of the normal children and unsatisfactory in two (cases 46 and 48). The increase in B.M.R. varied from 21 to 36%. The maximum rate was observed on the 2nd to the 6th day and the rate returned to the normal level by the 6th to the 17th day.

Dwarfs. The effects of the injection of 2 mg. or of 5 mg. of thyroxin upon the cholesterolemia and creatinuria of 3 dwarfs with retarded osseous development (*Group A*), and 2 dwarfs with normal osseous development (*Group B*), were similar to those found in normal children. In no case was there a sensitive response suggestive of hypothyroidism.

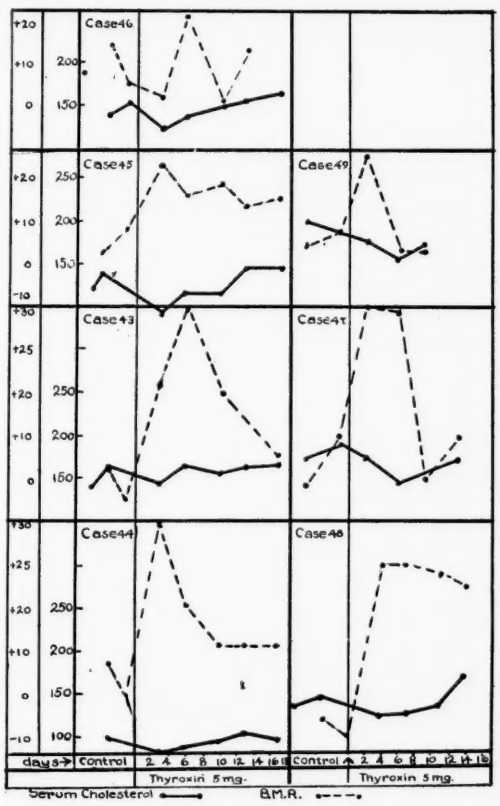

Fig. 4. NORMAL CHILDREN. EFFECT OF A SINGLE DOSE OF THYROXIN ON B.M.R. AND SERUM CHOLESTEROL.

DISCUSSION

The study of the response to the daily oral administration of thyroid, or to the injection of a single dose of thyroxin, showed that the effect upon the serum cholesterol serves better to differentiate the hypothyroid from the normal child than does the change in the creatinuria. It should be pointed out also that the studies of cholesterol can be carried out easily without hospitalization, whereas the creatine studies require hospitalization, special diet and the quantitative collection of urine over a long period.

With a daily dose of 2 grains (128 mg.) of desiccated thyroid, the serum cholesterol of hypothyroid patients decreased 117 to 385 mg.%, and, with a single dose of 2 mg. or 5 mg. of thyroxin, 120 to 229 mg. %. In marked contrast, the decrease in normal children was 0 to 76 mg.%, which was within the range of spontaneous fluctuations. The cholesterol response to a single dose of thyroxin showed an even more striking contrast between the hypothyroid and normal children than did the effect of the daily oral dosage, because the duration as well as the magnitude of the response could be studied. It is probable that 5 mg. of thyroxin serves better as a test dose than 2 mg., because the effect of 2 mg. on the cholesterol in one hypothyroid child (*case 40*) was open to doubt.

In studying the effect of standard doses of thyroid or of thyroxin upon the creatine excretion, a sharp contrast in the sensitivity of hypothyroid and of control children was not noted uniformly. This was due to the fact that the daily oral administration of ½ grain (32 mg.) of thyroid caused an increase of creatinuria in 6 of 14 normal children (42.9%), and 2 grains (128 mg.) caused an increase in 17 of 22 control cases (77.3%). The injection of thyroxin increased the creatinuria in 3 dwarfs of *Groups A* and *B*, but failed to do so in two other dwarfs of *Group A* and in one normal boy. It seems, therefore, that creatinuria is a more delicate indicator of thyroid effect in normal children than is cholesterolemia. In a subsequent study to be reported, we have used creatinuria as a measurement of the effect of the injection of thyrotropic hormone upon thyroid activity.

It is not clear why some normal children excrete increased quantities of creatine after the administra-

tion of thyroid and some do not. We have pointed out that the children who did not show a significant increase were those who had low levels of spontaneous creatinuria. It is possible that normal children or dwarfed children may actually have differences in their sensitivity to thyroid. However, it is not justifiable to make this assumption, because other factors than thyroid may influence the excretion of creatine.

Very little is known concerning the mechanism by which the thyroid hormone influences the serum cholesterol or the creatine excretion. A fact which is of some interest is that the effect of continuous thyroid administration upon the serum cholesterol is long continued, whereas the increased excretion of creatine is of relatively short duration even in hypothyroid patients. Shorr, Richardson and Mansfield (7) found that when constant daily doses of thyroid were given to a myxedematous adult, the creatine excretion rose rapidly to a high level, but that after several weeks the excretion began to decrease, returning almost to the base level after 40 to 60 days. Our experience has been the same in hypothyroid children. A similar observation was made by Carson (7a) in a normal person. The creatinuria usually increased abruptly by the second to the fifth day, but after one to two weeks it frequently decreased to a slightly lower level at which it remained fairly constant, with only a gradual decrease over a number of weeks. In normal children, the increase in the creatine excretion was sometimes very transient, lasting for only several days, while in other cases it was sustained for longer periods. These differences are illustrated by the cases shown in figure 1. The cause of the decrease in the creatine excretion after the sudden initial increase is not certain. It is possible that the creatine metabolism of the hypothyroid patient is especially sensitive at the beginning of thyroid administration, but becomes rapidly adjusted. This rapid adjustment of creatine metabolism can hardly be interpreted as an acquisition of increased tolerance to thyroid, as Shorr, Richardson and Mansfield (7) did not find a decreasing B.M.R. in myxedematous adults under treatment at the time that the creatine excretion was decreasing; and because, in our hypothyroid cases, the decreased creatine excretion was not accompanied by a rise in the serum cholesterol. Another possible explanation is that thyroid medication causes a washing out of stores of creatine or its precursors from the tissues, and that these stores are greater and less rapidly depleted in the hypothyroid than in the normal child. Perhaps studies of muscle creatine might shed some light on this problem.

It is not the purpose of this paper to discuss the etiology of dwarfism. However, observations have been made on 9 dwarfs (*cases* 29 to 32 and 50 to 54) who did not show characteristic physical signs of hypothyroidism, although a number of them had marked retardation of osseous development. Seven of the dwarfs have subsequently been treated with thyroid without significant acceleration of growth. In no was there a marked sensitivity to small doses of thyroid or to a single dose of thyroxin such as was found in the hypothyroid children. The creatine and cholesterol responses were not distinguishable from those of normal children. No differences were found between dwarfs with retarded and those with normal osseous development. Although the investigations revealed no evidence of hypothyroidism in the 9 dwarfs reported, this does not exclude the possibility that thyroid deficiency may be present in some dwarfs who do not present the characteristic clinical picture.

SUMMARY

The determination of the serum cholesterol and of the creatine excretion was used to measure the sensitivity of response to thyroid in hypothyroid and in normal children. The study of the response to small daily oral doses of thyroid or to a single injection of thyroxin showed that the effect upon the serum cholesterol served better to differentiate the hypothyroid from the normal child than did the increase in creatinuria.

With a daily dose of 2 grains (128 mg.) of desiccated thyroid, the serum cholesterol of hypothyroid patients decreased 117 to 385 mg.% and, with a single dose of 2 mg. or 5 mg. of thyroxin, 120 to 229 mg.%. The decrease in normal children was 0 to 76 mg.%, which was within the range of spontaneous fluctuations. With a single dose of thyroxin, the effect lasted an average of 38 days in hypothyroid children, and 9 days in normal children.

In hypothyroid children daily doses of thyroid as small as ½ grain (32 mg.) uniformly caused an increase in the creatine excretion. This same dose caused increased creatinuria in 42.8% of normal children, and 2 grains (128 mg.) daily caused an increase in 77.3%. Therefore, creatinuria is a more delicate indicator of thyroid effect in normal children than is cholesterolemia.

The results suggest that normal children may have differences in their sensitivity to thyroid. However, other possible interpretations are discussed.

Nine dwarfs who showed no evidences of hypothyroidism showed cholesterol and creatine responses to thyroid identical with those of normal children. There were no differences between dwarfs with retarded osseous development and those with normal development.

We wish to thank Dr. Eva Landsberg for her assistance in the creatine studies, and Dr. Hugh Josephs for making cholesterol determinations in conjunction with studies on blood fats, carotene and vitamin A to be reported later. Diets were planned and super-

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THE GASTRIC MOTILITY IN CERTAIN PATIENTS WITH THYROID DEFICIENCY[1]

HYPOTHYROIDISM

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GASTROINTESTINAL SYMPTOMS are often observed in patients presenting hyperthyroidism, but there have been few reports on the occasional association of abdominal distress with hypothyroidism. A review of the literature reveals several clinical warnings that hypothyroidism may be complicated by an abdominal pain which may even simulate various surgical entities; however, the mechanism of this pain is rarely discussed.

Hinton (1) finds that a comparatively small group of hypothyroid patients complain of abdominal discomfort. These are of interest to the clinician, however, because in addition to the occasional difficulty in making a diagnosis, the patients may be unnecessarily subjected to laparotomy. Lester (2, 3) has drawn attention to the number of appendectomies accomplished for chronic appendicitis, while the actual cause of the right lower quadrant pain appeared to be insufficient thyroid secretion. He states that, although less common, the abdominal distress which at times accompanies hypothyroidism may resemble the pain usually associated with peptic ulcer or cholecystitis. Further, cases are on record in which the patient was operated for intestinal obstruction when the cause of the distress was an imbalance due to hypothyroidism.

In an equally important but less dramatic fashion, other investigators have called attention to the abdominal symptoms observed in certain hypothyroid patients. Barker (4) relates a case of achylia gastrica, chronic diarrhea and anemia in a patient with congenital hypothyroidism. Dorff (5) describes a 6-year-old boy who exhibited dwarfism, an atonic intestinal tract, anemia and retarded osseous development, all due to hypothyroidism. Brown (6) reviewed the effect of hypothyroidism on gastric and intestinal function in 156 cases and concluded that there is no characteristic gastrointestinal picture. He found, however, that in certain of the patients hypothyroidism had played a considerable part in the development of intractable constipation and gastric subacidity.

Michael Wohl (7) studied 7 hypothyroid patients who complained of abdominal discomfort. Their complaints varied from vague abdominal distress to shooting pains in the abdomen, lumbar region or shoulders. There was no special reference to any particular organ; however, all the patients were constipated, and in all clinical improvement was noted following the administration of desiccated thyroid. Recently Bassler (8) described 3 patients with masked hypothyroidism presenting abdominal symptoms, and concluded: "Why there is abdominal pain or tenderness in this condition is not understood. It may be neurogenic in origin; it certainly is not due to colonic stasis or constipation."

The Surgical Research group at the Ohio State University have investigated the relation of gastric motility to hypothyroidism in 8 patients, 4 of whom we present at this time. The diagnosis was based on low blood iodine determinations and decreased basal metabolic rates, which along with the clinical findings was interpreted as hypothyroidism. All of these patients complained of indefinite abdominal distress for which no organic basis could be found. The abdominal discomfort was characterized chiefly by pain in the epigastrium, lower abdomen or right lower abdominal quadrant. Further, the pain varied in intensity from a vague, ill-defined abdominal discomfort to mild colic. In each of these patients, however, gastric hypermotility was observed simultaneously with the clinical evidence of abdominal pain regardless of its location or intensity. Appropriate thyroid and iodine therapy was subsequently instituted in each case. In 3 patients additional motility observations were

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[2] Comly Fellow in Research Surgery.

made after response to such treatment. In these 3, the return to a normal basal metabolism was accompanied by a normal gastric motility and the absence of abdominal discomfort.

The purpose of this paper is to present certain features of the mechanism and control of abdominal discomfort in 4 patients with hypothyroidism who presented gastrointestinal symptoms.

METHOD

The motility of the stomach was recorded by the balloon and kymograph method previously used in our clinic, as described by Barron, Curtis and Haverfield (9) and modified by Veach (10). The gastric motility graphs were analyzed according to MacQuigg's 8-type classification (11). The blood iodine determinations were made by analyzing the amount of iodine in 25 cc. of whole blood. For this the Matthews' modification of the Leipert method was used (12). The normal iodine content of whole blood, using this method, varies around four gamma per cent.

To illustrate the relationship of gastric hypermotility to the abdominal discomfort occasionally observed in hypothyroidism, we present studies on 4 patients. Follow-up studies are presented on 3 of these after they responded to treatment for hypothyroidism.

CASE REPORTS

Case 1. W.H., a white male, aged 26, was studied in the Out Patient Department. He complained of nervousness and dull, occasionally colic-like lower abdominal pain. There was clinical evidence of hypothryoidism. The physical examination result was negative. The laboratory examination results were negative except for a basal metabolism of −12 on 9/20/39; of −18 on 11/8/39; and −15 on 12/16/39. The whole blood iodine on 9/30/39 was 3.2γ%.

A gastric motility determination was accomplished on 10/2/39. During the entire study the stomach remained in low tonus, but exhibited continuous irregular activity with frequent type 5 contractions (table 1, fig. 1). Throughout the period of study the patient was aware of the same cramping lower abdominal pain of which he frequently complained.

On 10/4/39 another gastric motility determination was accomplished. The stomach showed a higher tonus, with continuous irregular activity consisting largely of type 4 motility (table 1, fig. 2). The individual gastric contrac-

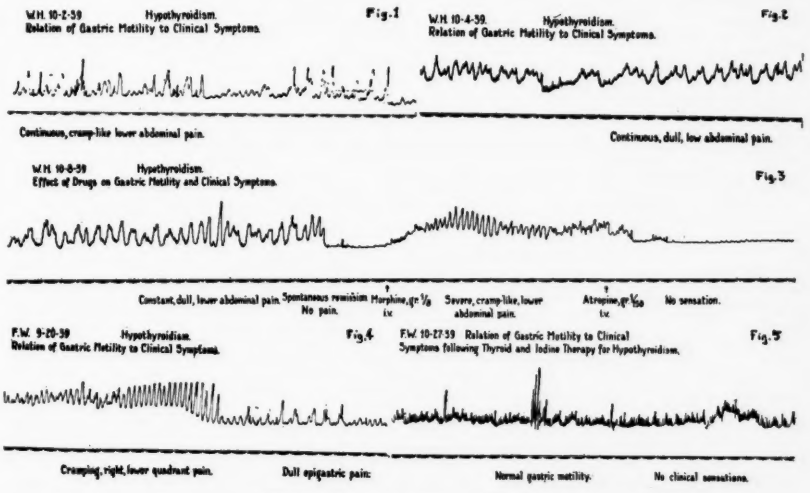
W.H. 10-2-39 Hypothyroidism. Fig. 1
Relation of Gastric Motility to Clinical Symptoms.
Continuous, cramp-like lower abdominal pain.
W.H. 10-4-39 Hypothyroidism. Fig. 2
Relation of Gastric Motility to Clinical Symptoms.
Continuous, dull, low abdominal pain.
W.H. 10-8-39 Hypothyroidism. Fig. 3
Effect of Drugs on Gastric Motility and Clinical Symptoms.
Constant, dull, lower abdominal pain. Spontaneous remission No pain. Morphine, gr 1/8 i.v. Severe, cramp-like, lower abdominal pain. Atropine, gr 1/150 i.v. No sensation.
F.W. 9-20-39 Hypothyroidism. Fig. 4
Relation of Gastric Motility to Clinical Symptoms.
F.W. 10-27-39 Relation of Gastric Motility to Clinical Symptoms following Thyroid and Iodine Therapy for Hypothyroidism. Fig. 5
Cramping, right, lower quadrant pain.
Dull epigastric pain.
Normal gastric motility.
No clinical sensations.

Fig. 1–5. GASTRIC MOTILITY RECORDS.

tions were less high than during the first study, and throughout this investigation, the patient complained of continuous, dull, lower abdominal pain.

On 10/8/39 a third gastric motility determination was accomplished on this patient. At the beginning of the study, the findings were similar to those recorded during the previous determinations (table 1, fig. 3). The stomach was in continuous irregular activity and the patient complained of constant, dull, lower abdominal distress. A spontaneous remission of activity then occurred, marked by a lowered tonus and gastric quiescence. During this period he noticed no unpleasant abdominal symptoms. Morphine gr. 1/8 was administered intravenously to activate the stomach. The usual motility response was noted at once, consisting of a rise in tonus, on which were superimposed gastric contractions (10). Simultaneously with the increased gastric activity, the patient complained of severe, cramp-like lower abdominal pains. Administration of atropine gr. 1/150 intravenously, inhibited the gastric activity, as shown by a lowered tonus and complete gastric quiescence. Simultaneously with the onset of gastric quiescence the patient was relieved of the lower abdominal pain, and had no unpleasant clinical sensations for the duration of the effect of the drug (table 1, fig. 3).

Case 2. F.W., a white male, aged 28, was admitted to

TABLE 1. W.H.

Complaints:—"Nervousness and lower abdominal pain." B.M.R. −12, −18. Blood iodine 3.2γ%.

	Type	Length	Ave. Ton.	No. cont.	No. cont. of max. amp.	Max. Inter.	Remarks
		Min.	Mm.		Range, Mm.	Min.	
Fig. 1. 10/2/39	3, 5	52.3	15	53	3 of 35–46	4.0	Continuous cramp-like lower abdominal pain.
Fig. 2. 10/4/39	4	27.2	33	30	4 of 21–24	2.5	Irregular tonus.
	7	7.7	47	23	4 of 18–20	0	Continuous, dull, lower abdominal pain.
Fig. 3. 10/8/39	4, 5	23.7	38	34	Max. of 48	0	Constant, dull, lower abdominal pain.
	Q	4.3	34	—	—	—	Spontaneous remission; no pain.
	7	16.0	55	—	8 of 19–24	0	M.S. gr 1/8 I.V. Severe colic.
	Q	18.3	40	—	—	—	At. S. gr 1/150 I.V. Relief of pain.

TABLE 2. F.W.

Complaints:—Colic-like rt. lower quadrant pain, occasional dull, persistent epigastric pain. B.M.R. −15, −12. Blood iodine 3.4; 3.3; 2.8; 2.9γ%.

Fig. 4. 9/20/39	6	16.6	47	43	19 of 21–40	0	Cramping R.L.Q. pain.
	5M	20.0	29	35	7 of 15–26	1.0	Dull epigastric pain.
			After treatment of hypothyroidism; no complaints, B.M.R. +4.				
Fig. 5. 10/27/39	2	46	31	29	Max. of 50	4.0	Normal gastric motility. No clinical sensations

TABLE 3. F.P.

Complaints:—Flatulence, distention, epigastric pain. B.M.R. −30.

Fig. 6a. 4/12/39	6	15.9	45	22	5 of 35–58	0	Constant epigastric pain.
	5	14.3	40	12	4 of 45–46	3.0	
	2	14.0	41	31	Max. of 10	0	Spontaneous remission; no pain.
Fig. 6b. 4/12/39	5	5.7	43	3	Max. of 42	3.2	
	6	4.0	45	7	Max. of 72	0	M.S. gr 1/8 I.V. Colic like epigastric pain.
	7	3.7	60	9	Max. of 45	0	
	Q	7.7	43	—	—	—	At. S. gr 1/150 I.V. Relief of pain.
			After treatment of hypothyroidism; no complaints. B.M.R. +2.				
Fig. 7. 6/5/39	4	45.5	37	84	Max. of 27	1.6	Normal gastric motility. No clinical sensations.

TABLE 4. B.H.

Complaints:—Constipation, epigastric pain. B.M.R. −12. Blood iodine 2.7γ%.

Fig. 8. 6/20/39	5	24.4	43	26	Max. of 24	2.8	Dull epigastric pain, with cramps at 4 peaks. (see fig. 8).
Fig. 9. 6/21/39	5	7.3	64	7	Max. of 37	.7	Colic like epigastric pain.
	6	7.2	59	12	9 of 25–43	0	
	Q	8.3	51	—	—	—	At. S. gr 1/150 I.V. Relief of pain.
			After treatment of hypothyroidism; no complaints. B.M.R. +1.				
Fig. 10. 8/2/39	2	45.0	46	?	Max. of 13	0	Normal gastric motility. No clinical sensations.

the University Hospital for the repair of an uncomplicated inguinal hernia. Investigation, however, revealed evidence of hypothyroidism, associated with frequent attacks of abdominal pain, located at times in the right lower quadrant, occasionally in the epigastrium. No organic basis could be found for this pain. The laboratory findings were negative except for a basal metabolism of −15 on 9/19/39, and −12 on 9/20/39. The whole blood iodine on 9/19/39 was 3.4γ%; 9/22/39, 3.3γ%; 9/23/39, 2.8γ%; and 9/26/39, 2.9γ%.

At the beginning of a gastric motility study on 9/20/39, the stomach was in high tonus and continuous activity, types 4 and 6 (table 2, fig. 4). During this period the patient complained of cramping right lower quadrant pain, clinically identical with the pain the patient had previously noted. This period was terminated by a fall in tonus

and decreased gastric activity, type 3. A change in clinical symptoms was associated with this alteration in gastric motility. For the duration of the type 3 activity, the patient noted the dull epigastric pain to which he was often subject, while there was a remission of the right lower quadrant pain.

Following repair of the hernia, the patient was treated for hypothyroidism by the administration of desiccated thyroid and iodine. The clinical response was satisfactory. On 10/27/39 the basal metabolism was +4, and he no longer complained of abdominal pain.

and during the entire period of gastric quiescence the patient remained free from pain. The period of spontaneous remission of activity observable in figure 6a persisted for approximately 2 hours. The period was terminated by the administration of the usual drugs in order better to observe the relation of gastric motility to clinical symptoms.

At the point indicated on figure 6b, morphine gr. 1/8 was administered intravenously to activate the stomach, and simultaneously with the increased tonus and gastric activity the patient experienced severe, colic-like epigastric

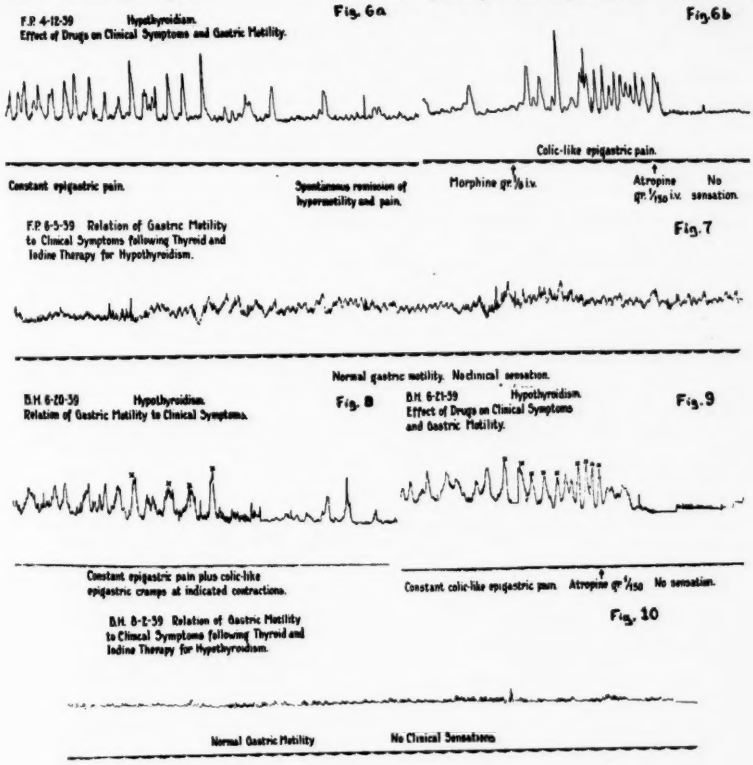
Fig. 6a
Fig. 6b
F.P. 4-12-39 Hypothyroidism.
Effect of Drugs on Clinical Symptoms and Gastric Motility.
Colic-like epigastric pain.
Constant epigastric pain.
Spontaneous remission of hypermotility and pain.
Morphine gr. 1/8 i.v.
Atropine gr. 1/150 i.v.
No sensation.
F.P. 6-5-39 Relation of Gastric Motility to Clinical Symptoms following Thyroid and Iodine Therapy for Hypothyroidism.
Fig. 7
Normal gastric motility. No clinical sensation.
B.H. 6-20-39 Hypothyroidism.
Relation of Gastric Motility to Clinical Symptoms.
Fig. 8
B.H. 6-21-39 Hypothyroidism.
Effect of Drugs on Clinical Symptoms and Gastric Motility.
Fig. 9
Constant epigastric pain plus colic-like epigastric cramps at indicated contractions.
Constant colic-like epigastric pain.
Atropine gr. 1/150
No sensation.
B.H. 8-2-39 Relation of Gastric Motility to Clinical Symptoms following Thyroid and Iodine Therapy for Hypothyroidism.
Fig. 10
Normal Gastric Motility
No Clinical Sensations

Fig. 6–10. GASTRIC MOTILITY RECORDS.

A gastric motility study on 10/27/39 showed the stomach to be in normal activity, with a moderate tonus (table 2, fig. 5). Throughout the study the patient had no unpleasant clinical symptoms. There has been no evidence of recurrence of the symptoms up to the present time.

Case 3. F.P., a white male, aged 48, was admitted to the University Hospital complaining of occasional attacks of epigastric pain, accompanied by flatulence and distention. Investigation revealed clinical evidence of hypothyroidism without disclosing an organic basis for the pain. The basal metabolism was −30 on 4/11/39.

At the beginning of a gastric motility study on 4/12/39, the stomach was in constant activity, type 5 (table 3, fig. 6a). During this period the patient complained of the same dull epigastric pain to which he had become accustomed. Soon a spontaneous remission of gastric activity occurred, pain. Atropine gr. 1/150 was administered intravenously, and at once the stomach became quiescent with simultaneous relief of the pain.

Since no organic basis could be found to account for the abdominal pain the patient was treated for hypothyroidism, by administration of desiccated thyroid and iodine. Following a satisfactory clinical response to treatment, the patient returned for study on 6/5/39.

The basal metabolism was plus 2 on 6/5/39. The same day a gastric motility study revealed normal stomach activity, and throughout the investigation the patient had no unpleasant abdominal sensations (table 3. fig. 7). There has been no evidence of recurrence of the clinical symptoms up to the present.

Case 4. B.H., a white female, aged 41, was admitted to University Hospital complaining of constipation and

frequent attacks of epigastric pain, variable in onset, duration and intensity. Investigation did not reveal any organic basis for the pain, but indicated clinical evidence of hypothyroidism. Laboratory investigation showed low gastric acidity, a basal metabolism of −12 on 6/20/39, and a whole blood iodine of 2.77% on 6/24/39.

A gastric motility study on 6/20/39 demonstrated hypermotility of the stomach, type 5, accompanied by dull epigastric pain, which the patient identified as the same type of pain she frequently observed (table 4, fig. 8). In addition, during this study the patient complained of severe, colic-like epigastric pain simultaneously with the 4 contractions indicated on figure 8.

On 6/21/39 a gastric motility study revealed somewhat similar findings. At the beginning of the study the stomach was in constant hyperactivity and the patient complained of dull epigastric pain (table 4, fig. 9). At the peaks of the 9 contractions indicated on the chart, the patient complained of severe colic-like epigastric pain similar in nature to the occasional epigastric colic of which she had complained on admission. At this time atropine gr. 1/150 was administered intravenously, and simultaneously with the resultant gastric quiescence the patient was relieved from all unpleasant clinical symptoms.

Since no organic basis could be found to account for the pain, the patient was treated for hypothyroidism by the administration of desiccated thyroid and iodine. Following a satisfactory clinical response to treatment, the patient returned for study.

On 8/2/39 the basal metabolism was plus 1. The same day a gastric motility study revealed normal stomach activity and throughout the investigation the patient had no unpleasant clinical symptoms (table 4, fig. 10). There has been no evidence of a recurrence of the abdominal discomfort up to the present.

DISCUSSION

Four patients have been studied who presented low blood iodine determinations and decreased basal metabolic rates, which along with the clinical symptoms was interpreted as due to hypothyroidism. In addition, all of these patients complained of abdominal pain which varied in extent, duration, intensity and position.

Gastric motility studies on each of these patients indicated that hypermotility of the stomach occurred simultaneously with clinical evidence of abdominal pain. When the stomach was quiescent the patients had no abdominal discomfort. This relief from abdominal distress was noted whether a spontaneous remission of gastric activity occurred, or the quiescence was induced by the administration of atropine. Further, in certain cases the inactive stomach was stimulated to hypermotility by the administration of morphine. Simultaneously with the onset of gastric hypermotility the patients again complained of abdominal pain, but were relieved following inactivation of the stomach by the administration of atropine.

Desiccated thyroid and iodine therapy was subsequently instituted in each case. In 3 patients we made additional motility observations after response to this treatment. In these 3, the return to a normal basal metabolism was accompanied by normal gastric motility and the absence of abdominal pain.

SUMMARY

A study of four patients who presented clinical evidence of hypothyroidism along with abdominal discomfort, shows that the abdominal pain is closely associated with gastric hypermotility. In three of these patients appropriate therapy for the hypothyroidism was followed by return of the basal metabolism to normal, return of the gastric motility to normal and relief from the abdominal pain.

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THYROID THERAPY IN GASTROINTESTINAL DISTURBANCES

THE USE OF THYROID SUBSTANCE IN CERTAIN GASTROINTESTINAL DISTURBANCES

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THYROID SUBSTANCE has proved of such benefit in certain gastrointestinal disturbances that it is felt this form of therapy deserves emphasis, particularly in view of the fact that many of these patients have submitted to surgery without benefit. This report is based on a study of 32 patients.

The gastrointestinal symptoms complained of were: sour eructations, nausea, belching of gas, and distress in various parts of the abdomen.

In addition to the symptoms enumerated, 24, or 75%, complained of periodic headache. The latter symptom was not as a rule accompanied by vomiting, aura, scotomata, or other symptoms found in migraine. That a close relationship existed between the headache and real migraine is shown by the fact that 19, or 59%, had a familial history of migraine.

The abdominal distress in some patients simulated peptic ulcer, the pain coming on from ½ to 2 hours after meals. Sour eructations, belching of gas and nausea were also outstanding symptoms.

Various forms of diet, including ulcer regimen with alkalies, antispasmodics, vitamins, and other forms of medication had been tried by many patients without improvement.

Of the 32 patients, 23, or 72%, were female and 9, or 28%, were male.

Eleven patients, or 34%, had had an appendectomy for chronic appendicitis. Since the symptoms continued, the operation may be considered a failure. Eight patients, or 25%, had a diagnosis of chronic appendicitis made by the roentgenologist but were not operated upon.

In regard to the frequent performance of appendectomy in these patients, as well as the frequency of migraine, an article in which I reviewed 100 cases of migraine is of interest (1 a). Therein it was stated:

> From the data in regard to laparotomies, one may conclude that an operation for so-called chronic appendicitis is often performed and unfortunately with no relief. I was impressed with the fact that many of the patients invariably stressed the abdominal symptoms of their trouble. Twenty per cent of the 100 cases had had primary appendectomies for chronic appendicitis, and in addition 9 cases had had a fluoroscopic diagnosis of chronic appendicitis but had not been operated upon. The lesson to be learned from this is that great care must be exercised in performing laparotomies on migrainous patients, and this becomes particularly important in those subjects who have abortive attacks of migraine.

In this regard a recent article by Alvarez (2) is of interest. He called attention to the numerous failures of appendectomy in curing patients with the diagnosis of chronic appendicitis. He said,

> On studying the histories of 385 patients, who, some years before, in their home cities, had submitted to appendectomy, I found that only 2, or 0.8% of the 255 who had never had an acute attack of appendicitis were cured, while 87, or 67%, of the 130 who had had at least one acute attack of abdominal pain, were cured.

In the data of 255 patients who gave no history of acute appendicitis, he lists 24 who had migraine, or a migraine equivalent, showing that the condition under discussion is not uncommon and is frequently confused with chronic appendicitis.

The basal metabolism ranged from 0 to minus 23%, the average basal metabolic rate being minus 15%.

The cholesterol values on 15 patients ranged from 150 mg. to 330 mg. per 100 cc., the average being 237.7 mg. (Sackett's modification of Bloor's method). This is similar to averages found in 27 cases of migraine previously reported (225 mg.).

Thirteen, or 40%, had enlargement of the thyroid gland; in addition to these, 3 had had thyroidectomy for a toxic adenomatous goiter.

Because of the history of headache and familial migraine in several patients, the elevated blood cholesterol and the low basal metabolic rate, small doses of desiccated thyroid, grains ¼ (0.015) 3 times a day were given. Improvement usually followed within a week after beginning therapy. The headache and gastrointestinal symptoms disappeared. The length of time that the thyroid therapy was continued varied. After 3 weeks usually the daily dose

was decreased to one tablet, grains ¼ (0.015) a day.

Symptoms of overdosage such as return of headache, nervousness, tachycardia, and insomnia were indications to discontinue the therapy. It was again resumed within 2 or 3 weeks in the single daily dose of grains ¼ (0.015).

Those patients with thyroid enlargement should be watched carefully for symptoms of toxicity since they are more readily made toxic than those without thyroid enlargement.

Bassler (3) has recently reported 3 cases of masked hypothyroidism with abdominal symptoms consisting of abdominal pain simulating gastro-duodenal ulcer, cholecystitis and appendicitis. These cases were relieved by thyroid therapy. His patients presented low blood pressure, leukopenia and a low basal metabolic rate.

In my series the blood pressure was normal in most instances, the range being from 96 systolic to 236 systolic and 60 diastolic to 140 diastolic, the average being 119 systolic and 77 diastolic. No case of leukopenia was encountered, although lymphocytosis was frequently present.

No doubt the cases reported in this article are of the same type as those reported by Bassler. Gastroenterologists must see this condition more frequently than other specialists. That surgeons do is shown by the high percentage of patients who had appendectomy. Bassler (3) quotes Ramsey as saying that in myxedema, the gastrointestinal symptoms are "anorexia, flatulence (especially after meals), constipation, occasional nausea and rare vomiting, gastric hypoacidity and achlorhydria, and abdominal pains which may simulate gastro-duodenal ulcer, cholecystitis and appendicitis."

In the present series no striking classical hypothyroid signs were present. A subnormal temperature, dry skin, and brittle nails were present in some patients. A few complained of vertigo, a symptom that is not infrequently found in hypothyroid individuals, and some complained of ringing in the ears, another symptom frequently seen in hypothyroidism (1 b).

Twenty-two, or 68.7%, of the patients reported improvement in their symptoms following thyroid therapy. The digestive symptoms disappeared, constipation improved, and they felt better generally. The headache also disappeared.

Ten, or 31%, were not improved, in fact thyroid therapy made them worse and I cannot help but feel that the thyroid condition (and in some cases the adenoma) was activated by the therapy. Care must be taken, therefore, in giving thyroid substance to these individuals over a period of time for fear of activating the thyroid.

I am of the opinion that these patients who have thyroid adenomas with a low basal metabolic rate are made worse by thyroid therapy and are best treated by thyroidectomy. While none of the patients in the present series who failed to respond had a thyroidectomy, elsewhere (1 c) I reported on the benefits of thyroidectomy in the presence of a normal or low basal metabolic rate. Three patients of the present series had had a thyroidectomy for a toxic goiter and developed the gastrointestinal symptoms subsequent to operation.

Until the etiology is better understood, it is useless to speculate as to why thyroid therapy benefits these patients. As mentioned previously, hypothyroid individuals have gastrointestinal symptoms similar to those herein mentioned.

The most likely explanation for the thyroid influence on the amelioration of symptoms seems to me to be this gland's relationship to the central nervous regulating mechanism, and more particularly to the hypothalamicohypophyseal system.

The thyroid's influence on the central nervous system is well known (4, 5, 6). Its relationship to the hypothalamus has also been investigated. More recently Sheehan (7) has shown the influence of the hypothalamus on gastrointestinal regulation. This would suggest that the benefits in the cases under discussion may be achieved by way of this mechanism. Certainly a trial of thyroid therapy would seem worth trying before submitting a patient to operation for chronic appendicitis, especially if the patient has periodic headaches and a familial history of migraine. Basal metabolism and blood cholesterol studies should be made in doubtful cases. It is to be noted that the blood cholesterol is elevated in hypothyroidism and in the cases under discussion; so that thyroid therapy is logical.

SUMMARY

Thirty-two cases having certain gastrointestinal disturbances are reported. The symptoms simulate peptic ulcer, chronic cholecystitis, chronic appendicitis, and mucous colitis. Seventy-five per cent of the patients had periodic headaches; 59% had a familial history of migraine; 34% had an appendectomy for chronic appendicitis without relief of symptoms.

There was an elevated blood cholesterol (average 237.7 mg.). The average basal metabolic rate was minus 15%.

Twenty-two, or 68.7%, were relieved of their symptoms by thyroid therapy, while 10, or 31%, were not improved.

The possibility of the thyroid-central nervous system relationship, and more particularly the thyroid-hypothalamic-gastrointestinal relationship may explain the reason that thyroid therapy benefits the majority of these patients. Care should be exercised in operating on patients with gastrointestinal disturbances and basal metabolic and blood cholesterol studies should be made in doubtful cases.

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PARATHYROID THERAPY

DIHYDROTACHYSTEROL (A.T. 10) AND MINERAL METABOLISM; A METABOLIC STUDY

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SINCE 1933 when Holtz (1) introduced the substance A.T.10 (dihydrotachysterol) for the control of hypoparathyroid tetany, numerous reports have appeared in the foreign literature confirming his excellent results. Arnold and Blum (2) in 1936 were apparently the first to use A.T.10 in this country. They reported relief of all symptoms and a return of the serum calcium to normal in 28 cases. Three of these cases were so severe that they could not be maintained free from tetany or even convulsions by the usual methods of treatment, including large doses of vitamin D, intravenous calcium, low phosphorus diet, and parathyroid hormone. Since then reports (3, 4, 5) have been published which are in agreement with the excellent clinical results noted by foreign investigators.

All authors have demonstrated that dihydrotachysterol is an ideal drug for the treatment of tetany when certain precautions are kept in mind. In this regard they have stressed the importance of individualizing the dosage as only small amounts are necessary and each patient seems to have his own requirement. None have failed to warn against the harmful cumulative effects which may lead to hypercalcemia with its toxic symptoms or even to pathological calcification of various organs.

It was not until Albright and his associates (6) in 1938 published their studies on patients treated with dihydrotachysterol that the fundamental action of the the new drug on calcium and phosphorus metabolism was investigated. From observations on two patients with idiopathic hypoparathyroidism and one with postoperative hypoparathyroidism they concluded that the action of A.T.10 was similar to that of both vitamin D and the parathyroid hormone.

The purpose of this investigation is to study the calcium and phosphorus metabolism of two patients with hypoparathyroidism and a patient who developed tetany during the course of progressive renal failure due to chronic pyelonephritis. The result of A.T.10 therapy in these three cases may further clarify the pharmacology of this drug.

CASE REPORTS

Case 1. The first case was that of a 30-year-old man weighing 70 kg. (154 lb.). He had been in the hospital for two weeks in December 1936 when he was found to have a duodenal ulcer. Recovery from this was progressing satisfactorily until July 1937 when he caught "the grippe." During his convalescence he lost 30 lb. in weight and developed nervousness. These symptoms progressed and tremor appeared. He came to the hospital in January 1938 suffering from typical Graves' disease. Iodine administration induced a prompt remission and a sub-total thyroidectomy was performed Feb. 19, 1938. His postoperative course was uneventful and he was discarged on March 6, 1938 apparently well. After he returned home he began to notice a sensation of pins and needles in his arms, particularly after exertion. Although mild at first, in the next 6 weeks the sensations became much more intense and he was bothered by stiffness of his hands, cramps in his arms which would draw his hands up into peculiar positions, and a 'rolling' gait. He became almost incapacitated and returned to the hospital.

During the course of observation he was given a constant diet containing 1 gm. of calcium and 1 gm. of phosphorus per day. Calcium and phosphorus determinations were made on the output of 5-day periods.[1]

At the beginning of the study the serum calcium was 6.3 mg./100 cc., and serum phosphorus 5.9 mg./100 cc. During the two control periods the Chvostek and Trousseau signs were positive. He had paresthesias in various parts of his body and muscle

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[1] The urinary calcium was determined by the method of Shohl and Pedlay, *J. Biol. Chem.* 50: 537. The fecal calcium was determined by McCrudden's method, *J. Biol. Chem.* 10: 187. The phosphorus in the urine and feces was determined by the method of Fiske and Subarow, *J. Biol. Chem.* 66: 375.

cramps which were made more severe if he attempted any great activity.

On the first day of the third period he was given 10 cc. of A.T.10 (5 mg. of dihydrotachysterol per cc.)

TABLE 1. CASE 1.

Period	Intake	Calcium* Output Urine	Calcium* Output Feces	Balance	Serum Ca	Serum P
	gm.	gm.	gm.	gm.	mg./100 cc.	
I	1.017	0.015	0.668	+.334	6.3	5.9[1]
II	1.022	0.013	0.652	+.357	7.7	6.1[1]
III†	1.017	0.009	0.512	+.496	7.2	5.1[1]
					7.9	5.4[2]
					8.3	5.8[3]
					8.3	5.3[4]
IV	1.015	0.018	0.480	+.517	9.0	5.0[2]
					9.6	4.2[4]
V	1.017	0.022	0.454	+.541	10.7	4.8[1]
					9.8	4.2[4]
VI	1.019	0.013	0.612	+.394	9.6	4.9[1]
					9.6	5.8[5]
VII	1.010	0.022	0.568	+.420	9.8	5.4[5]

* Figures are average daily values for the period.

† A.T.10 therapy in Period III: 10 cc. (=50 mg.) on day 1; 5 cc. on day 2 and day 3.

[1 . . . 5] Superior numbers refer to day of period for which serum Ca and P values are given.

and 5 cc. on each of the succeeding two days. Fasting blood samples were drawn for serum calcium and phosphorus determinations before the drug was given on each of these days and at intervals thereafter. There was prompt relief of the symptoms. The Chvostek and Trousseau signs became negative and remained so. The studies were continued for the next four periods (20 days), and the changes which took place in the calcium and phosphorus balance are recorded in tables 1 and 2.

On discharge the patient was feeling well and had no symptoms or signs of tetany. He was given a high calcium diet and vitamin A and D tablets as the only therapy. Since the serum calcium had remained normal, it was felt that this regime would be adequate without the further use of A.T.10. On his weekly visits to the clinic he reported that he continued to feel perfectly healthy. He soon returned to work. During his visits blood was drawn for calcium and phosphorus determinations. For the next 3 months after discharge his serum calcium remained between 9.3 and 10.7 mg./100 cc , and his serum phosphorus between 4.6 and 6.0 mg./100 cc.

Case 2. The second patient was a 22-year-old white woman who had been in very good general health until November 1937. She then began to have nervousness, tremor, increased perspiration and exophthalmos. She lost 35 lb. in 8 months. She was admitted to the Surgical Service on June 1, 1938 presenting a typical picture of exophthalmic goiter. Her B.M.R. was +51. A sub-total thyroidectomy was performed on June 15. Three days after operation she noticed tingling of her hands and feet and Chvostek sign was positive. She was allowed to go home but the tingling became worse and she developed carpal and pedal spasms and dysphagia of such severity that readmission was necessary. This time treatment was instituted with calcium and parathyroid hormone and also small doses of A.T.10. Improvement was satisfactory and she was discharged on August 2, 1938. During her subsequent course tetany was fairly well controlled by calcium lactate by mouth and small doses of A.T.10.

In September she became pregnant. As the pregnancy progressed, increasing ankle edema, headaches, and shortness of breath were noted. In the seventh month she had to be admitted to the Obstetrical Service and labor induced on March 25, 1939 because of pre-eclampsic toxemia. After delivery she recovered; albuminuria disappeared, and her blood pressure returned to normal. The urea clearance test showed 50% of normal clearance and one month later 64% of normal clearance.

Two weeks after delivery she had a generalized convulsion for the first time. She was transferred to the Medical Service for regulation of her parathyroid insufficiency and study of her mineral metabolism.

TABLE 2. CASE 1.

Period	Intake	Phosphorus* Output Urine	Phosphorus* Output Feces	Balance	Serum Ca	Serum P
	gm.	gm.	gm.	gm.	mg./100 cc.	
I	1.076	0.466	0.382	+.228	6.3	5.9[1]
II	1.072	0.450	0.532	+.092	7.7	6.1[1]
III†	1.068	0.788	0.408	−.128	7.2	5.1[1]
					7.9	5.4[2]
					8.3	5.8[3]
					8.3	5.3[4]
IV	1.068	0.734	0.412	−.078	9.0	5.0[2]
					9.6	4.2[4]
V	1.068	0.650	0.320	+.098	10.7	4.8[1]
					9.8	4.2[4]
VI	1.068	0.605	0.420	+.044	9.6	4.9[1]
					9.6	5.8[5]
VII	1.065	0.655	0.372	+.038	9.8	5.4[5]

* Figures are average daily values for the period.

† A.T.10 therapy in Period III: 10 cc. (=50 mg.) on day 1; 5 cc. on day 2 and day 3.

[1 . . . 5] Superior numbers refer to day of period for which serum Ca and P values are given.

A diet was given containing 1 gm. of calcium and 1 gm. of phosphorus per day. This was constant throughout the six 5-day periods of study. Calcium and phosphorus determinations were made on the in-

take, urine, stool and blood, as in the previous case. After 3 control periods the effect of her previous therapy was considered to have disappeared. Her serum calcium had fallen to 7.4 mg. per 100 cc. and the serum phosphorus was 9.2 mg. per 100 cc. On the first day of the fourth period she received 10 cc. of A.T.10 and 5 cc. on each of the next 2 days. There was a rapid rise in the serum calcium to normal and a fall in the serum phosphorus. The numbness and tingling in her hands, present before therapy, disappeared and the Chvostek sign became negative. There was a decrease in the fecal calcium and an increase in the urinary phosphorus as shown in tables 3 and 4. After two more periods of observation she was allowed home on May 25, 1939.

Since discharge she has been followed in the clinic. She takes 3 gm. of calcium lactate daily and 5 cc. A.T.10 per week. This regime has been found satisfactory in maintaining her free from symptoms and signs of tetany. Blood calcium and phosphorus values are normal. Her general health has been excellent during this time.

Case 3. The third case was that of a 31-year-old woman weighing 60 kg. (132 lb.) who was admitted complaining of shortness of breath for 24 hours. She had had scarlet fever at 7 years of age but knew of no renal complications. She was in a hospital for pyelitis at 14 years of age and again the next year. There had been early morning headaches for 2 years previously. For a month before admission she had a non-productive cough. The week before she noticed an increase in the cough and shortness of breath on exertion. The day prior to admission she brought up some pink frothy sputum. The dyspnea became more severe and as she was verging on collapse she was brought to the hospital. Energetic treatment relieved her pulmonary edema and cardiac failure. However, she remained drowsy. The urea nitrogen was 60 mg.% and CO_2 combining power 41 vol.%. She was given intravenous fluids with considerable improvement. Hartman's solution (0.6 molar sodium lactate) was given with further beneficial effect. At this time she began to complain of tingling in her arms and legs, and a constricting feeling in her throat with occasional periods of a crowing noise on respiration. Her serum calcium was found to be 6 mg.% and serum phosphorus 7.6 mg.%, The symptoms were not constant and as she was improving generally the administration of Hartman's solution was continued. A few days later she developed fibrillary twitchings of her muscles and frank signs of tetany. The Trousseau and Chovstek signs became positive. The CO_2 combining power was found to be 63 vol.%, and the serum calcium 5.3 mg.% and serum phosphorus 6.4 mg.%. One hundred units of parathyroid hormone were administered at this time, resulting in complete relief of symptoms and signs of tetany in the following 24 hours.

TABLE 3. CASE 2.

Period	Intake	Calcium* Output Urine	Output Feces	Balance	Serum Ca	Serum P
	gm.	gm.	gm.	gm.	mg./100 cc.	
I	1.032	0.023	0.438	+.571	10.3	9.0^1
II	1.030	0.017	0.910	+.103	8.3	8.6^1
III	1.030	0.013	0.806	+.211	8.1	8.6^1
IV†	1.030	0.029	0.478	+.523	7.4	9.2^1
					8.8	9.4^3
					11.1	8.0^5
V	1.030	0.108	0.648	+.274	10.3	6.8^2
					9.5	7.2^4
VI	1.030	0.078	0.724	+.228	10.6	7.2^1
					9.9	6.6^5

* Figures are average daily values for the period.
† A.T.10 therapy in Period IV: 10 cc. (=50 mg.) on day 1; 5 cc. on days 2 and 3.
$^{1 \ldots 5}$ Superior numbers refer to day of period for which serum Ca and P values are given.

TABLE 4. CASE 2.

Period	Intake	Phosphorus* Output Urine	Output Feces	Balance	Serum Ca	Serum P
	gm.	gm.	gm.	gm.	mg./100 cc.	
I	1.228	0.502	0.236	+.490	10.3	9.0^1
II	1.222	0.555	0.432	+.235	8.3	8.6^1
III	1.222	0.575	0.396	+.251	8.1	8.6^1
IV†	1.222	0.867	0.225	+.130	7.4	9.2^1
					8.8	9.4^3
					11.1	8.0^5
V	1.222	0.754	0.296	+.172	10.3	6.8^2
					9.5	7.2^4
VI	1.222	0.790	0.290	+.142	10.6	7.2^1
					9.9	6.6^5

* Figures are average daily values for the period.
† A.T.10 therapy in Period IV: 10 cc. (=50 mg.) on day 1; 5 cc. on days 2 and 3.
$^{1 \ldots 5}$ Superior numbers refer to day of period for which serum Ca and P values are given.

For mineral balance studies she was transferred to the metabolism ward where she was given a constant diet containing 1 gm. of calcium and 1.2 gm. of phosphorus per day. Calcium and phosphorus balance determinations were carried out on 5-day periods the same as for the previous cases. She received no more intravenous fluids and her general condition remained quite satisfactory. She had no further symptoms of tetany and the Chvostek and Trousseau signs were negative. During the 3 control periods her serum calcium rose spontaneously from 5.6 mg.% to 7.7 mg.% and serum phosphorus from 5.6 mg.% to 8.8 mg.%. She received 10 cc. of A.T.10 at the beginning

of the fourth period and 5 cc. on each of the following two days (100 mg. total). During this and the next two periods there was so little change in her mineral balance that it was decided to increase the dosage. During the seventh period she received 35 cc. of A.T.10 (175 mg. total). The figures for the calcium and phosphorus balance are shown in tables 5 and 6.

TABLE 5. CASE 3.

Period	Intake	Calcium* Output Urine	Output Feces	Balance	Serum Ca	Serum P
	gm.	gm.	gm.	gm.	mg./100 cc.	
I	1.016	0.019	0.960	+.037	5.6	5.6[3]
II	1.012	0.020	0.748	+.244	8.5	8.6[1]
III	1.007	0.020	0.792	+.195	7.7	8.8[1]
IV†	1.009	0.019	0.680	+.310	7.5 8.8 8.5 8.8	8.4[1] 9.4[2] 10.2[3] 9.7[5]
V	1.016	0.021	0.680	+.315	9.0	10.0[4]
VI	1.017	0.018	0.542	+.457	8.6	11.2[5]
VII†	1.014	0.019	0.585	+.410		
VIII	1.018	0.023	0.360	+.635	9.1	11.6[1]

* Figures are average daily values for the period.

† A.T.10 therapy. Period IV: 10 cc. (=50 mg.) on day 1; 5 cc. on days 2 and 3. Period VII: 15 cc. (=75 mg.) on day 2; 10 cc. on days 3 and 4.

1 . . . 5 Superior numbers indicate day of period for which serum Ca and P values are given.

The urea nitrogen continued to be elevated between 60 and 90 mg.%, and the CO_2 combining power ranged from 30 to 50 vol.%. Her urine showed from 3+ to 1+ albumin, no sugar, and upon microscopic examination was found persistently loaded with white cells and clumps of white cells, but no red cells or casts.

These findings, in addition to a continued hypertension, anemia, and a urea clearance of 7.5% of normal standard in the first specimen and 6.5% of normal standard in the second specimen, pointed clearly to the diagnosis of chronic pyelonephritis in an advanced stage. She was discharged feeling quite well and able to be up and take care of herself. At home she did not do well. The renal insufficiency progressed and she returned two months later with terminal uremia and died. Autopsy revealed chronic pyelonephritis and changes in the organs associated with uremia. Unfortunately, the parathyroid glands could not be examined.

RESULTS

In the first patient with hypoparathyroid tetany, a positive balance of both calcium and phosphorus was maintained during the two control periods. In the third period, during which he received 20 cc. of A.T.10, there was a prompt and very marked increase in the urinary phosphorus as shown in table 2. This increase was sustained during the fourth period. It was sufficiently marked to cause the phosphorus balance to become negative during these periods. The fecal phosphorus remained essentially unchanged. The serum phosphorus, after an initial slight rise, fell to normal levels during the fourth and fifth periods.

In the fifth period the urinary phosphorus had returned to nearly its control level and it remained there during the sixth and seventh periods. During the sixth period the serum phosphorus rose to 5.8 mg./100 cc. and was 5.4 mg./100 cc. at the end of the seventh period. The changes brought about in the phosphorus metabolism by A.T.10 were of relatively short duration and at the end of two periods, when the phosphorus balance again became positive, the serum phosphorus also returned to its pre-therapy value.

Following the administration of the drug, there was a sharp decrease in the fecal calcium. Table 1 shows these results. The urinary calcium increased in the fourth period and continued to increase in the next period. There was an immediate and progressive rise in the serum calcium to within normal limits.

TABLE 6. CASE 3.

Period	Intake	Phosphorus* Output Urine	Output Feces	Balance	Serum Ca	Serum P
	gm.	gm.	gm.	gm.	mg./100 cc.	
I	1.288	0.391	0.648	+.249	5.6	5.6[3]
II	1.267	0.506	0.462	+.299	8.5	8.6[1]
III	1.206	0.475	0.460	+.271	7.7	8.8[1]
IV†	1.219	0.490	0.356	+.373	7.5 8.8 8.5 8.8	8.4[1] 9.4[2] 10.2[3] 9.7[5]
V	1.245	0.514	0.356	+.375	9.0	10.0[4]
VI	1.257	0.570	0.317	+.370	8.6	11.2[5]
VII†	1.137	0.560	0.306	+.271		
VIII	1.251	0.516	0.228	+.507	9.1	11.6[1]

* Figures are average daily values for the period.

† A.T.10 therapy. Period IV: 10 cc. (=50 mg.) on day 1; 5 cc. on days 2 and 3. Period VII: 15 cc. (=75 mg.) on day 2; 10 cc. on days 3 and 4.

1 . . . 5 Superior numbers indicate day of period for which serum Ca and P values are given.

The effect of the drug on the fecal calcium was of longer duration, but by the sixth period (15 days after therapy) it too had returned to its initial level. The urinary calcium continued at a value slightly higher than the control period level. This can be ex-

plained by the fact that after therapy the serum calcium remained in the normal range.

The second patient with hypoparathyroid tetany showed changes in mineral balance similar to those of the previous case. There was a positive calcium and phosphorus balance during the 3 control periods, which became less positive in both instances as the result of previous therapy wore off (tables 3, 4). Following administration of 20 cc. of A.T.10 in the fourth period, there was a sharp rise in urinary phosphorus as shown in table 4. Although the phosphorus balance did not become negative, in this period, as it did in the first case, it became much less positive. The excretion of phosphorus in the urine remained well above the control values during the next two periods. With these changes, there was a fall in the serum phosphorus from 9.2 mg. per 100 cc. to 6.6 mg. per 100 cc. at the end of the experiment.

As observed in the first patient, there was also a marked decrease in the fecal calcium value following administration of A.T.10. These results are shown in table 3. The serum calcium rose to 11.1 mg. per 100 cc. on the fifth day of the fourth period and in the subsequent periods the urinary calcium output was markedly increased.

In the case of the third patient with tetany secondary to chronic pyelonephritis, there was a positive calcium and phosphorus balance during the 3 control periods, as shown in tables 5 and 6. The serum calcium rose from 5.6 mg. per 100 cc. to 8.6 mg. per 100 cc. in the second period and then fell to 7.7 mg. per 100 cc. in the third period. The serum phosphorus rose from an initial value of 5.6 mg. per 100 cc. to 8.6 mg. per 100 cc. and then to 8.8 mg. per 100 cc. in the third period.

In the fourth period she received 20 cc. of A.T.10 (100 mg.). While the serum calcium rose to 8.8 mg. per 100 cc. there was no change in the urinary calcium and only a slight decrease in the fecal calcium.

In the seventh period 35 cc. of A.T.10 (175 mg.) was given. Again there was no essential change in urinary calcium. The fecal calcium, which had been decreasing slowly throughout the period of observation, fell more sharply in the period following the administration of this large dose. Meanwhile the serum calcium had risen progressively until it was 9.1 mg. per 100 cc. at the end of the experiment.

The phosphorus metabolism was noteworthy for the fact that the balance remained positive despite large amounts of A.T.10. The urinary phosphorus increased steadily throughout the period of observation. There was no significant change following either dose. The fecal phosphorus decreased steadily and the serum phosphorus rose from 5.6 mg. per 100 cc. at the onset to 11.6 mg. per 100 cc. at the end of the experiment. Thus, the phosphorus metabolism in this case seemed to be entirely unresponsive to the changes which A.T.10 is capable of producing as demonstrated in the first two patients.

DISCUSSION

The results in the first two cases show that in hypoparathyroid tetany, A.T.10 produces a marked increase in urinary phosphorus excretion which was associated with a return of the serum phosphorus to normal. This is in agreement with the aforementioned work of Albright and his associates (6).

The parathyroid hormone has been shown to have an exactly similar action on phosphorus metabolism by Albright, Bauer, Ropes and Aub (7). They showed in addition that this hormone produces an increase in the serum calcium and in the urinary calcium by removing calcium from the bones. In this respect, A.T.10 differs greatly. These two cases demonstrate that A.T.10 causes an increase in the absorption of calcium from the intestinal tract. Albright and Sulkowitch (8) demonstrated that vitamin D has a similar effect on calcium metabolism, but the effect takes place less rapidly than with A.T.10 (6).

Consideration of the case of tetany secondary to chronic pyelonephritis reveals a striking contrast in the response of the phosphorus metabolism to treatment with A.T.10. There was practically no increase in urinary phosphorus in response to the medication and the serum phosphorus rose steadily to reach a peak of 11.6 mg./100 cc. just after the largest dose was given. There was, however, a progressive decrease in the fecal calcium indicating increased absorption. This differed from the preceding cases in that there was no sudden change which could be correlated with the administration of the drug but rather a slow decrease throughout the whole experiment.

A further contrast is shown in the urinary calcium values. In the cases of hypoparathyroidism, there was a slight increase in urinary calcium following the increased absorption and return of the serum calcium to normal. There was no change at all in the urinary calcium in the third case.

The explanation for these differences lies primarily in the fact that this case had such advanced renal damage that additional phosphorus excretion was impossible. Of secondary importance are the parathyroid glands which were probably undergoing hypertrophy in response to the increasing phosphorus retention. Their action might obscure to some extent the changes for which A.T.10 would otherwise have been responsible.

Some mention must be made of the prolonged elevation of the serum calcium in the first case after the effect of A.T.10 had disappeared. That the A.T.10 no longer exerted any influence was evidenced by a return of the fecal calcium to the control period level

and the cessation of its effect on the phosphorus metabolism. The explanation for this is not clear. It is possible that some functioning parathyroid tissue remained after operation. During the period of observation it may have undergone sufficient hypertrophy so that its secretion was enough to maintain a normal serum calcium. The return of the phosphorus levels in the blood and urine to their pre-therapy values speaks against this theory but is not conclusive evidence. There is nothing to support further speculation on this point.

SUMMARY

A.T.10 produces an increase in the renal excretion of phosphorus with a consequent lowering of the serum phosphorus in parathyroid deficiency. With extreme kidney damage there is impaired phosphorus excretion which is not changed by A.T.10. A.T.10 causes an increase in absorption of calcium from the intestinal tract with a resulting rise in serum calcium.

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TREATMENT OF EUNUCHOIDISM

IMPLANTATION OF TESTOSTERONE COMPOUNDS IN CASES OF MALE EUNUCHOIDISM[1]

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THE EFFECTIVENESS of an endocrine preparation is measured best by its capacity to restore normal function in a characteristic endocrinopathy caused by its deficiency. Eunuchoidism, or male hypogonadism, is the clinical state in which the primary deficiency resides in the testes, and therefore it represents an ideal clinical condition for testing the effectiveness of an androgenic substance.

The synthesis of testosterone by Butenandt and Hanisch (1) and Ruzicka et al. (2) made available for the first time a male hormone which could be tested clinically. Numerous observers have found this substance and its propionic acid ester to possess striking therapeutic value. The history and bibliography of this subject have been adequately reviewed in a recent paper by Vest and Howard (3) and also in a monograph by Moore and Koch (4). These reports have described the good results following parenteral injections of testosterone in an oily vehicle, 2 to 7 times weekly. In our own experience, most eunuchoids have responded satisfactorily to doses of 25 mg. of testosterone propionate injected 3 times each week, although a few of the very severe cases have required daily treatments.

Since this is essentially 'replacement' or 'substitution' therapy, such frequent injections for an indefinite period soon become an annoyance and an expensive burden. Therefore the reports of Deanesly (5) and of Deanesly and Parkes (6) concerning the effectiveness of implanted tablets of the pure sex hormone aroused considerable interest. The possibility of administration at longer intervals and of better utilization presented obvious advantages. The successful application of this method has been confirmed by Vest and Howard (7, 8) and by Eidelsberg and Ornstein (9) who used pellets of pure crystalline testosterone in treating eunuchoids. Other workers have also reported experience with this method of treatment (10, 11).

Our own experience in 7 characteristic cases seems worthy of record because: first, crystals of methyl testosterone and testosterone propionate were used; furthermore, the method of preparation of these pellets as recently modified by one of us (G. R. B) is some what simpler than the procedures previously employed; and finally, the implantation of hormone crystals is still a relatively novel therapeutic strategy and recorded experiences from different groups of workers seem clearly desirable.

TECHNICAL METHODS

The mold for the preparation of the pellets is made of hardened steel and bolted to a machined flat steel block (fig. 1, 2). It contains 36 holes, each 5 mm. in depth and 1.83 mm. in diameter. The crystalline testosterone preparation,[2] in the form of powder, is packed into the holes and then compressed by a die consisting of 36 plungers which fit snugly into each hole. A pressure of 6500 lb. per square inch is applied in a hydraulic press. The pellets are forced out by removing the flat steel block and pushing the plungers completely through the mold (fig. 2A). A receptable beneath catches the pellets, each of which weighs between 8 and 11 mg., averaging 9 mg. Those used at the beginning of this study were of a smaller type, the preparation of which was described in previous publications (12, 13, 14).

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[2] The crystalline methyl testosterone and testosterone propionate were supplied through the courtesy of Dr. E. Oppenheimer and Dr. R. C. Mautner of the Ciba Pharmaceutical Products, Inc.

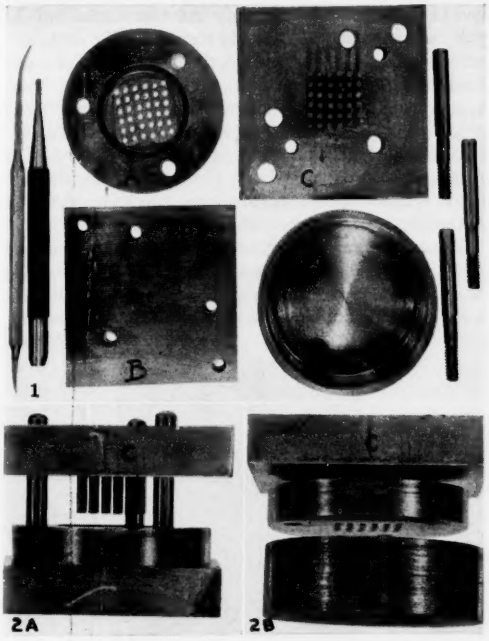

Fig. 1. COMPONENTS OF THE PELLET MACHINE. (a) mold; (b) flat steel plate with machine ground surface; (c) die with plungers corresponding to holes in mold; (d) receptacle. Fig. 2A. PELLET MACHINE ASSEMBLED AND READY FOR COMPRESSION AFTER THE POWDERED CRYSTALLINE ANDROGEN HAS BEEN PACKED IN THE HOLES. (a) mold; (b) flat steel plate; (c) die. Fig. 2B. PELLET MACHINE PARTIALLY DISASSEMBLED AFTER COMPRESSION, READY FOR EXPULSION OF THE PELLETS. (a) mold; (c) die; (d) receptacle.

After weighing, the pellets are prepared for administration by placing the required number in the lumen of a number 12 needle. The point is loosely corked and a fairly snug-fitting stylet closes the other end. The loaded needle is then placed in a test tube and sterilized in the pressure autoclave for 20 minutes at 120°C. and under a pressure of 15 lb. per square inch. The site for the implant, either on the arm or on the thigh, is prepared by sterilization of the skin followed by the infiltration of a small area with novocaine. A small incision is then made, and after removing the cork, the needle is inserted into the subcutaneous tissue for a distance of 4 or 5 cm. The pellets are left under the skin by withdrawing the needle on the stylet (fig. 3).

Discussion of technic. Sterilization in the pressure autoclave requires a compound with a high melting point so that the pellets will remain separate and will not be altered in shape. Methyl testosterone and testosterone are satisfactory in this regard, as their melting points are 163–4°C. and 154–5°C. respectively. Since testosterone propionate melts at 121–3°C., the pellets of this substance must be sterilized in an Arnold autoclave over a period of 3 days.

Studies of absorption from the pellets, made in experimental animals, indicate that the important factors are: the surface area of the pellets exposed to the tissues, the degree to which the hormone crystals have been compressed, and the physical nature of the compound. Pellets of all crystalline steroid compounds when implanted into body tissues cause a low-grade inflammatory reaction which results in the formation of a fibrous capsule around the pellets. Blood and lymphatic capillaries appear in the capsules, as well as some lymphocytes and an occasional giant cell. Absorption takes place through the capillaries at a rate probably proportional to the size of the surface area. The degree of compression in the apparatus described is practically constant; the variations due to this factor are therefore excluded. Previous observations have indicated that less compact pellets are absorbed more rapidly. The rate of absorption does not seem to be influenced by the solubility of the compound in various chemical solvents, nor by its melting point. Observations in animals in respect to pellets of methyl testosterone, in which all factors are constant except the surface area, show that absorption takes place almost equally from all surfaces, that small variations in size and weight have only a slight influence on the daily amount absorbed and that the amount absorbed daily slowly decreases.

When injected in an oily vehicle in test animals, the most effective compound of testosterone is the propionate, next in order is the methyl ether form, while the free form is the least effective (15). The clinical effectiveness of methyl testosterone, as reported below, indicates that the slow, uniform absorption from pellets may alter this relationship. Further observations on this problem are in progress.

The amount of methyl testosterone administered was at first arbitrarily set at approximately 100 mg. distributed in about 20 pellets. This amount has proved to be effective, but in later implants with larger pellets a total dose of 140 to 180 mg. was given in an attempt to prolong the effect. Experimental ob-

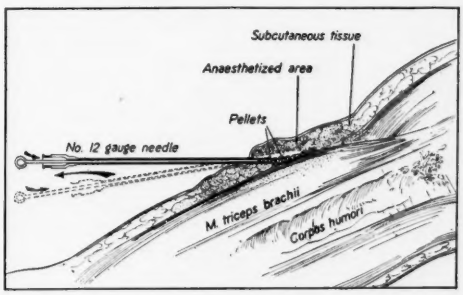

Fig. 3. DIAGRAMMATIC ILLUSTRATION OF INSERTION OF PELLETS INTO SUBCUTANEOUS TISSUES.

servations (16) have indicated that the average daily absorption from each pellet varied from 0.1 to 0.17 mg. so that the total average daily absorption varied from 2 to 3 mg. In some instances, however, the rate must have been slower, because effects from a single implant of about 100 mg. have lasted as long as 9 weeks. Waning effectiveness just before the pellets vanish completely suggests some decrease in the average daily absorption.

TABLE 1. THE IMPLANTATION OF METHYL TESTOSTERONE PELLETS

Case No.	Date	Amount implanted	No. of pellets implanted	Duration of effect
		mg.		*days*
1	10/26/39	100.3[1]	14	79
	1/11/40	83.2	18	70
	3/21/40	103.7	20	42
	5/ 2/40	149.4[2]	17	—
2	11/30/39	125.0	20	36
	1/ 4/40	98.5	20	42
	3/21/40	105.6	20	—
3	11/30/39	101.0	23	63
	3/21/40	105.6	20	48
	5/15/40	147.3[2]	17	—
4	2/ 1/40	102.7	18	50
	3/21/40	111.2	20	55
	5/15/40	148.0[2]	17	—
5	2/ 1/40	103.4	19	50
	3/21/40	100.7	20	35
	4/25/40	160.0[2]	17	32
	5/27/40	152.2[2]	17	—
6	3/21/40	109.6	20	55
	5/15/40	138.3[2]	16	—
7	4/17/40	180.1[2]	19	33
	5/27/40	147.6[2]	17	—

[1] Testosterone propionate pellets.
[2] Larger methyl testosterone pellets.

Case Histories

Case 1. W.C., (*U49328*) (fig. 4), a 31-year-old migrant was first seen in the University of California Clinic Aug. 23, 1939. Ten years previously he had sustained a severe skull fracture following which he had been unconscious for 17 hours. He then had had convulsions 2 to 12 times daily until 4 years before when a section of his skull was removed surgically. This resulted in some diminution in frequency and severity of the 'spells.' He had taken phenobarbital for 10 years. His genitalia had always been small, but he had possessed fair sexual function until the accident. After this his libido diminished gradually, nocturnal emissions ceased and he had been impotent for the preceding 5 years. He still had occasional partial erections and was shaving at approximately 2-week intervals.

At time of examination the patient weighed 147½ lb. and was tall with disproportionately long extremities. He looked younger than his age and had a high-pitched voice. Blood pressure was 105 systolic and 70 diastolic. The skin was of fine texture. The axillary hair was normal but the pubic escutcheon was typically feminine. The penis was small, measuring 5¾ cm. in length and 8½ cm. in circumference. The testes were small and soft, the right being approximately 2 by 1 cm. and the left 3 by 1½ cm. Rectal palpation indicated a small prostate. Laboratory investigations revealed a B.M.R. of −23%, and a bone age of 22 to 23 years (chronological age, 31 years). No creatin[3] was found in the urine. No urinary androgens were detectable in the urine collected for 3 consecutive days.[4]

Treatment was begun Oct. 26, 1939, with the implantation of 14 pellets of testosterone propionate, totalling 100.3 mg. The patient had 4 convulsive attacks in the next 2 days, but then they ceased for about 9 weeks. However,

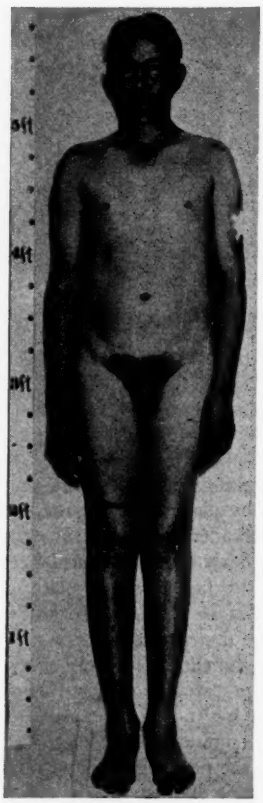

Fig. 4. *Case 1*, primary hypogonadism; age 31. Note disproportionately long extremities, small genitalia and feminine pubic escutcheon. See text for response to testosterone implants.

[3] Children of both sexes and the adult female excrete creatin in the urine. It was formerly believed that the adult male does not, but this has recently been contested. The presence of creatin in adult male urine has been considered indicative of hypogonadism.

[4] All androgen determinations were performed in the Institute of Experimental Biology, University of California, through the courtesy of Dr. Herbert M. Evans. The method of extraction described by Gallagher et al. (17) was used. Assays were made by a modification of the baby chick method as described by Burrows et al. (18) and by Frank and Klempner (19).

the site of the implant in the left upper arm became infected and began to discharge purulent material in a few days. This continued intermittently for several weeks as a result of which some of the implanted material was undoubtedly lost. This period was complicated by the unavoidable removal of 6 infected teeth and the subsequent development of purulent sinusitis. In spite of these vicissitudes there was a definite improvement in sexual status manifested by erections nearly every day and a general increase in strength and vigor. About 9 weeks after the implantation (during the sinusitis) the patient discontinued the phenobarbital for 2½ days, resulting in 10 epileptic seizures within 24 hours. At that time he began to note a definite diminution of libido and frequency of erections so that at the end of another week he had had only one erection, and three convulsive attacks had occurred. His penis at that time measured 8½ cm. in length, which represented a growth of about 3 cm.; the testes remained the same size.

Fig. 5. *Case 2*, adult hypogonadism; age 43. Note feminized adiposity and eunuchoid fat pads in outer portion of upper eyelids. Genitalia are somewhat atrophic, pubic hair is sparse and of feminine type. See text for response to testosterone implants.

Another implant was administered on Jan. 11, 1940, 2½ months after the first, the dose being 83.2 mg. of methyl testosterone distributed in 18 pellets. The convulsive attacks then ceased and the patient's strength improved. Libido returned and erections occurred daily. Five weeks later he reported that he was shaving 2 to 3 times each week, whereas formerly shaving had been necessary only once in 2 weeks. His penis and testes were approximately the same size. The B.M.R. was −25%, the bone age showed complete epiphyseal union, urine androgens were detectable in the amount of 1 I.U. per day. He still had occasional convulsions, usually when he had neglected to take phenobarbital.

A third implant was given on March 21, 1940, consisting of 103.7 mg. of methyl testosterone in 20 pellets. Just prior to this, erections had occurred less frequently. This implant resulted in an increased number of erections but the epileptiform seizures continued. There was a noticeable diminution of effect after about 5 weeks.

A fourth implant was given on May 2, 1940, consisting of 149.4 mg. of methyl testosterone in 17 pellets. At his last visit 11 days later, the patient again reported an increased number of erections and one nocturnal emission. At this time the penis measured 8¼ cm. in length and 9 cm. in circumference, and the testes were 2½ by 1½ and 3½ by 2 cm. on the right and the left respectively. These measurements represented some growth of both the penis and the testes.

Case 2. V.N., (*U31605*) (fig. 5), a 42-year-old white Russian masseur, was first seen in the University of California Clinic in May, 1938. The family history revealed that two siblings had had toxic goiters. In the preceding 7 months the patient had lost 32 lb. and had had weakness and vertigo. Libido had waned and he had become impotent. During this time he had lost hair from the chest and the pubic region.

Examination showed an enlarged thyroid and some atrophy of the penis and testes. His B.M.R. was +38% and later +30%; the plasma cholesterol was 183 mg.%. In July 1938 a subtotal thyroidectomy was performed because of a hyperplastic thyroid gland. Two months later he had regained 18 lb., but complained of weakness, stiffness of the joints, loss of head hair, and of feeling cold continuously. His B.M.R. was −22% and plasma cholesterol was 303 mg.%. After another 2 months' period he had further gained 11 lb. and, because of postoperative hypothyroidism was given desiccated thyroid. This caused headaches and swelling of the face; so thyroxyl was substituted. Later he was able to tolerate desiccated thyroid made by a different firm, which was much cheaper than thyroxyl. On this preparation he felt better generally, but there was no return of libido or potentia. He had occasional hot flashes and nocturnal emissions occurred about every 2 months. At this time (April, 1939), in spite of previously having been "strong sexually," he had been unable to have intercourse for 1½ years. His skin had become fine in texture and the loss of hair had continued.

Examination showed him to look older than his years and his skin was finely wrinkled. There were fat pads in the outer portions of the upper eyelids, a characteristic of hypogonadism. The hair on the head was gray and of fine texture. There was no hair on the trunk or the extremities and the pubic hair had a feminine distribution. The penis and scrotum were somewhat small, the former measuring 8 cm. in length and 9¼ cm. in circumference. The right testicle measured 3½ by 2½ cm. and the left 3 by 2½ cm. The B.M.R. was then −4%, the glucose toler-

ance curve was flat and the sella turcica appeared normal in an x-ray of the head. Androgens were estimated in a 3-day urine sample and 20 I.U. per day were found (normal range, 25 to 50). The patient's weight varied from 210 to 215 lb. and his blood pressure was 120 systolic and 70 diastolic.

On November 30, 1939, 125 mg. of methyl testosterone in 20 pellets were implanted. Soon thereafter the patient felt stronger, had occasional erections, and in 5 weeks had had 2 nocturnal emissions. However, he was still unable to have intercourse, so on January 4, 1940 (5 weeks later), he was given another implant of 98.5 mg. in 20 pellets in the opposite arm. After this the erections became more frequent, occurring once or twice daily, and the patient had successful intercourse twice in the following 3 weeks. Five weeks after the second implant he felt stronger and his beard was heavier. At this time he became somewhat more nervous, had some palpitation and lost some weight, so that the dose of thyroid had to be reduced. There had been a slight increase in axillary hair. The penis now measured 8½ cm. with a circumference of 9 cm. and the testes measured 4 by 3 and 4 by 2½ cm. on the right and left respectively. A rectal examination indicated a prostate less than one-fourth normal size.

One week later (6 weeks after the implant) the patient reported a definite drop in libido and no more erections. The urine androgens were tested again and none were detected in a 3-day sample. His weight was 212 lb. and his blood pressure 120 systolic and 70 diastolic. His general strength remained good until the material was available for the next implant on March 25, 1940, when 20 pellets of methyl testosterone were administered, representing 105.6 mg.

At his last visit 2 months later the patient reported that he had had a marked effect from the implant for 1 month, with erections every day and nocturnal emissions about every 2 weeks. During the second month there had been some gradual diminution but he had had satisfactory intercourse 3 weeks before. A definite drop in libido had been apparent in the preceding few days. Beard and chest hair were much heavier so that daily shaving was necessary. His general strength was improved with the result that he had secured a much better position. His weight was now 217¼ lb. The penis measured 9 cm. in length (formerly 8 cm.) and 9¼ cm. in circumference and the testes measured 4½ by 3 cm. bilaterally (representing some increase in size). At this time (May 24, 1940) another implant of methyl testosterone was administered, totalling 153.8 mg. in 16 pellets.

Case 3. L.K. (U20634) (fig. 6, 6A, 6B), a 24-year-old butcher was seen in September, 1937. He had had occasional erections and sexual dreams since he was 10 years of age and had tried masturbation, but he had never achieved an emission. An operation for bilateral undescended testicles had been attempted when he was 16 years old and at that time the left testicle was found to be almost completely atrophic. He had never shaved and had grown 1 inch in the preceding year.

The patient was 71¾ inches tall with disproportionately long arms and legs. He weighed 146 lb. and his blood pressure was 110 systolic and 80 diastolic. His

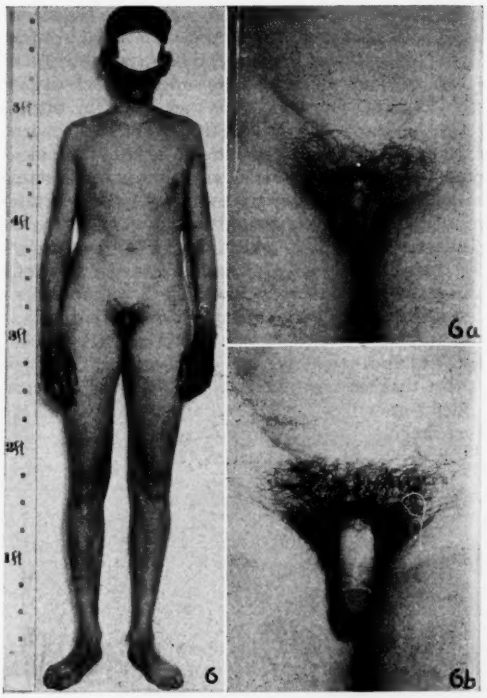

Fig. 6. *Case 3*, typical pre-adolescent eunuchoid (primary hypogonadism); age 25. Before treatment. Note disproportionately long extremities, broad pelvis, childish genitalia and sparse pubic hair. Has never shaved. Voice still high pitched. Fig. 6A. *Case 3*, before treatment; age 25. Note scars from operation at the age of 16 for cryptorchidism. No definite testicular tissue palpated. Fig. 6B. *Case 3*; age 27. After 21½ months' treatment with testosterone injections and implants. Note striking growth of penis and increased amount of pubic hair.

voice was high pitched and he looked younger than his age. A few axillary hairs were present and the pubic hair was sparse. The penis was small, measuring 4¾ cm. in length and the only scrotal content was some questionable tissue on the left. There was possibly some testicular tissue in the inguinal canals. Laboratory examination revealed a B.M.R. of −4%, a rather flat glucose tolerance curve, urinary creatin of 430 mg.%, and a bone age of 15 years (as compared to the chronological age of 24).

Treatment was begun with the equine gonadotropic hormone[5] in doses of ½ to 4 cc. 3 times weekly for 4 months. The patient reported a slightly increased number of erections, but the genitalia were unchanged in appearance and there were no other effects. At this time a small amount of prostatic tissue could be felt.

The patient was then given testosterone propionate[6] hypodermically in doses of 10 mg. 3 times weekly. After 4 months of somewhat irregular administration, he reported that he felt much improved. On the night of the

[5] Gonadin, kindly furnished by the Cutter Laboratories, Berkeley.

[6] Perandren, kindly furnished by the Ciba Pharmaceutical Products, Inc.

first injection he had had a spontaneous orgasm without emission and later he had had a nocturnal emission. He shaved each week and the penis was larger, measuring 5½ cm. in length. The dose was then increased to 25 mg. 3 times weekly. This was administered fairly regularly for 11 months and resulted in more frequent erections, occasional nocturnal emissions and occasional masturbation. His voice was deeper, he had gained 20 lb., and his general strength and feeling of well-being improved. His height had increased ¾ of an inch to 72½ inches. The blood pressure was unchanged, being 110 systolic and 60 diastolic. The breasts were somewhat fuller and hair growth had increased so that there now was a normal amount of axillary hair and a moderate pubic escutcheon. The penis measured 8 cm. in length, a growth of over 3 cm., and was 10 cm. in circumference. The testes now were palpable—bean-sized on the right and the size of a small olive on the left. The bone age was 19 years (an increase of 4 years in 2 years' elapsed time); the urinary creatin was 864 mg.

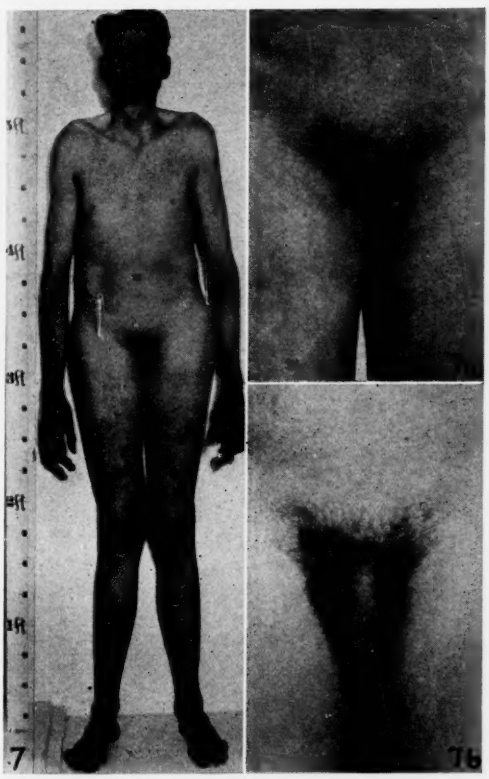

Fig. 7. *Case 4*, typical primary hypogonadism; age 31; before treatment. Note characteristic eunuchoid proportions with long arms and legs and broad pelvis; tiny genitalia, very sparse pubic hair. Had never shaved; voice high pitched. Fig. 7A. *Case 4*. Before treatment; age 31; testes size of pine-nuts, prostate not palpable. Note feminine contour of thighs. Fig. 7B. *Case 4*, age 33; after 17 months of treatment with testosterone injections and implants. Note marked growth of penis and increased amount of pubic hair.

On Nov. 30, 1939, the injections were stopped and 23 pellets of methyl testosterone, totalling 101 mg., were implanted subcutaneously. Seven weeks later the patient reported continued improvement with maintenance of the former sexual status. He was still having erections each day and occasional nocturnal emissions. His penis was larger, being 8½ cm. long and 9 cm. in circumference. Eleven weeks after the implant the patient reported that he had had a urinary infection, probably a pyelitis, requiring treatment with sulfanilamide, and for 2 weeks had noticed diminished libido and infrequent erections. A 3-day urine sample at this time showed only 1 I.U. of androgen excreted daily. Five weeks later the urinary infection had cleared, but there had been no return of libido. His general strength remained good. He weighed 165½ lb., and the blood pressure was 120 systolic and 70 diastolic. The penis was unchanged, but the testes were somewhat larger. Both were at the upper poles of the scrotum. The prostate was about one-fourth normal size.

At this time (March 21, 1940) another implant was given consisting of 105.6 mg. of methyl testosterone compressed into 20 pellets. This caused a return of libido and erections, reaching a peak at 16 to 19 days. Definite diminution of effect was noted 7 weeks after the implant. On May 15, 1940 (after an 8-week interval), the patient measured 72 7/8 inches, a further increase of 3/8 of an inch in height within 6 months; his weight was 170 lb., a gain of 4 lb. in the same length of time. His penis now measured 9 cm. in length (a growth of 1 cm. since the start of implantation therapy) and the circumference was 9¼ cm. The testes were slightly larger. At this time another implant was given, totalling 147.3 mg. of methyl testosterone in 17 pellets.

Case 4. J.J. (*U36521*) (fig. 7, 7A, 7B), A 31-year-old railway freight handler came to the University of California Clinic in May, 1938. His family history revealed that his mother and one sister had been confined in mental hospitals and that one brother was subject to spells of epilepsy. The patient had done poorly in school and had had epileptiform seizures from the age of 16. These had gradually diminished in frequency since the age of 25 and had been completely absent for 2 years.

The patient had never developed sexually, but had had some libido and had tried masturbation frequently without ever having an orgasm. Intercourse had been attempted unsuccessfully 8 to 10 times since the age of 21, and at the last attempt, 1 year previously, he had contracted gonorrhea. During the preceding 2 years he had developed a small amount of axillary and pubic hair, but his beard was only a fuzz which was clipped every 2 or 3 weeks.

On examination he looked decidedly younger than his age and exhibited the typical eunuchoid disproportionately long extremities. His height was 71 inches and his weight 133 lb. His voice was high pitched and the skin smooth and slightly wrinkled. The blood pressure was 120 systolic and 75 diastolic. Two to six axillary hairs were present on each side and there was a fair amount of pubic hair. The penis was small, measuring 4½ cm. in length (about normal for a 5-year-old boy),

and the testes in a small scrotum were very small. No prostatic tissue could be felt by rectum. B.M.R. was −7% and the plasma cholesterol 190 mg.%; the bone age was 18 years (compared to a chronological age of 31); no androgens were detected in complete urine specimens for 3 consecutive days; no urinary creatin was present.

In October, 1938, the patient was started on equine gonadotropic hormone[7] and received this in doses of ½ to 2 cc. (100 to 400 U) thrice weekly for 3 months. As a result of this, erections occurred with slightly increased frequency, but masturbation remained unsuccessful. His penis was unchanged, but the scrotum and testes became somewhat larger. At the end of 3 months, the right testicle measured 3 by 1½ cm. and the left 2 by 1 cm. (a definite increase in size). Again no prostatic tissue could be felt. Urinary androgens were re-tested in a 3-day specimen and 21 I.U. per day were present (normal 25–50). He now weighed 137½ lb., a gain of 4½ lb.

The patient was then started on testosterone propionate. At first 10 mg. was given and the dose was increased shortly to 25 mg. 3 times weekly at which level it was continued for 1 year. He had immediate prolonged erections, and after 1 month commenced to have emissions. After 3 months, he performed sexual intercourse successfully for the first time. At the end of 1 year he was having 2 to 5 erections daily and was masturbating twice weekly. In addition he was able to have intercourse about every 2 weeks. His general strength and appearance had improved and there was a definite increase of axillary and pubic hair. The beard was reported to be growing somewhat faster, but still only required "cutting" every 2 or 3 weeks. The epileptic seizures had returned about the middle of the year while the patient was away on a trip. He continued to have these about once each month.

Examination at the end of the year showed him to be 71¼ inches in height and to weigh 152 lb., a further gain of 14½ lb. The blood pressure had not changed, being 120 systolic and 80 diastolic. His penis now measured 8 cm. in length (formerly 4½ cm.) and the testes were somewhat smaller (right 2 by 1 cm., and left 1½ by 1 cm.). The prostate could now be felt and was approximately half the normal size. The secretion was examined and was normal, but no spermatozoa were seen. His bone age at this time was 19 years (an increase of 1 year in 1 year), and urinary androgens were now 5 I.U. per day.

On Feb. 1, 1940, the hypodermic injections were discontinued and 18 pellets of methyl testosterone, totalling 102.7 mg., were implanted subcutaneously. Five weeks later the patient stated that his libido had increased and 7 weeks after the implant he reported that his beard was heavier and that no further "seizures" had occurred. At this time (March 21, 1940) a second implant was given, with a total dose of 111.2 mg. of methyl testosterone distributed in 20 pellets. Eight weeks later he reported continued sexual stimulation with some moderate decrease in the preceding week. At this time his height was 71⅜ inches (an increase of ⅜ of an inch in 17 months) and he weighed 151 lb. (a gain of 18 lb. in the same interval). His penis now measured 9 cm. in length and 8 cm. in circumference, having enlarged somewhat under implantation therapy. The testes were also slightly larger, measuring 2½ by 1½ on the right and 2 by 1 cm. on the left. At this time another implant was given, totalling 148 mg. of methyl testosterone in 17 pellets.

Case 5. A.H., (*U39262*) (fig. 8, 8A), a 26-year-old graduate student was first seen in the University of California Clinic in May, 1934, his chief complaint being "lack of development." The family history revealed that 1 sister was underdeveloped and that a brother had not grown pubic hair until the age of 17. The patient's genitalia had always been small and his testes had been migratory, being found in the scrotum and inguinal canals at different times. He had never experienced any libido, but had had occasional erections. His beard required shaving only at 2-week intervals.

Examination showed the patient to be a typical preadolescent eunuchoid 70½ inches in height with characteristic disproportionately long extremities. He weighed 118 lb. and the blood pressure was 130 systolic and 80 diastolic. Axillary hair was scant but there was a moderate amount of pubic hair. The penis and scrotum were small,

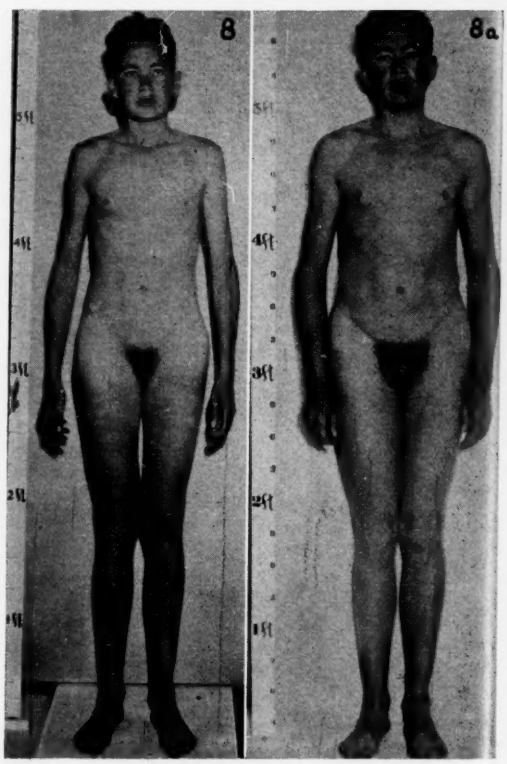

Fig. 8. *Case 5*, typical primary hypogonadism; age 26, looks much younger. Note disproportionately long extremities, relatively broad pelvis with feminine contour of thighs, minute genitalia and sparse pubic hair. Fig. 8A. *Case 5*, age 30; after 14 months of testosterone injections and implantations. Had gained 17 lb; more masculine build; rather heavy growth of pubic hair becoming masculine in distribution.

[7] Gonadin, kindly supplied by the Cutter Laboratories.

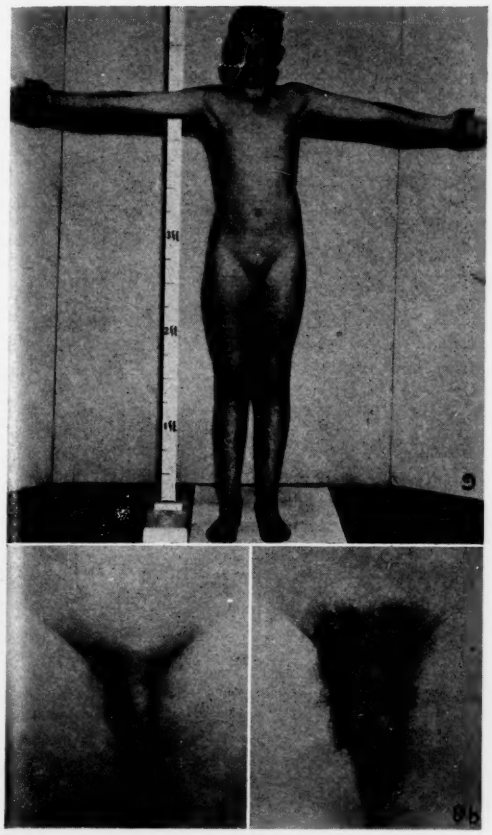

Fig. 9. *Case 6*, primary hypogonadism; age 17, looks younger. Genitalia infantile; no pubic or axillary hair; voice high pitched; no beard. Fig. 9A. *Case 6*, age 21. Appearance of genitalia (January 1937) after 3 months of very small doses of testosterone propionate (5 mg. 3 times weekly). Even this amount had produced a decided change. Fig. 9B. *Case 6*, age 24; after 3½ years' treatment with testosterone injections and implants. Genitalia now adult size.

the former being only 2½ cm. in length with an approximate circumference of a lead pencil, while the testes were the size of date seeds. No prostatic tissue could be felt. Laboratory examinations revealed a B.M.R. of −18% and a bone age of 14 years (chronological age, 26 years).

Previous treatment had been without effect and no endocrine therapy was prescribed, the male hormone not having been discovered at that time. However, the patient was seen again at the age of 30. He then weighed 133 lb. His sexual status was unchanged. Periodic migraine attacks were an additional complaint. At this time no urinary androgens could be detected in a urine sample collected over 3 consecutive days.

Treatment was begun 3 months later, in March, 1939, with testosterone propionate,[8] in a dose of 25 mg. 3 times weekly. After 4 months of treatment (50 doses) the patient showed marked improvement. He reported continuous priapism during the first week of treatment and frequent erections thereafter. The migraine attacks had disappeared; he had gained 15 lb., felt stronger and was shaving twice weekly. His voice had become considerably lower pitched and he noted also that his nipples were slightly sensitive. The penis now measured 3¾ cm. in length (formerly 2½ cm.) and 5¼ cm. in circumference. The testes were larger, each one being the size of a small olive. The B.M.R. was then −17% and the plasma cholesterol 303 mg.%.

Dosage was then increased by having the patient continue the injections of 25 mg. 3 times weekly with the addition of inunctions of testosterone propionate ointment,[9] 4 mg. nightly. After 2 months he reported no essential change subjectively, but the penis was larger measuring 4½ cm. in length and 7 cm. in circumference.

The testosterone propionate injections of 25 mg. 3 times weekly were taken more or less continuously for 11 months until February, 1940. At this time the patient was having 2 or 3 erections daily and occasional nocturnal emissions. His voice was deeper and there was a heavier growth of beard and body hair. The penis was 6 cm. in length and 6¾ cm. in circumference, and the testes each measured 2½ by 1½ cm. Semen had been obtained twice by masturbation and the second sample showed an increase in amount (1.2 cc.) and cellular content but no spermatozoa were seen. A recent B.M.R. had been −2% and plasma cholesterol 222 mg.%.

The patient then weighed 151½ lb., a gain of 18 lb., and his blood pressure was 115 systolic and 70 diastolic. As the genitalia were still quite small, it was decided to raise the dose still further. He was advised to continue injections of testosterone propionate in doses of 25 mg. 3 times weekly, and in addition 19 pellets of methyl testosterone, totalling 103.4 mg., were implanted subcutaneously. A definite increase in libido and in the number of erections resulted with the maximum effect about 10 days after the implant. Two and one-half days after the implant another 3-day urine sample was examined for androgens, and excretion of 18 I.U. per day was found (normal 25 to 50).

Four weeks after the implant the patient had to stop his hypodermic injections for 10 days and there was a definite diminution of libido which returned to some degree on resumption of injections. After 7 weeks the patient weighed 149 lb. and his blood pressure was 110 systolic and 70 diastolic. He was having 1 to 2 erections daily and the secretion from masturbation measured 1.8 cc. (the most observed). The prostate now was 1/3 normal size and the secretion appeared normal but without spermatozoa.

At this time (March 21, 1940) another implant was given with a total dose of 100.7 mg. of methyl testosterone distributed in 20 pellets. Following this the erections increased to 4 daily, but after 2 weeks the patient was forced to stop his injections of testosterone propionate for the following 3 weeks. This resulted in a markedly decreased number of erections. Another implant was given after a 5-week interval on April 25, 1940, the total dose being 160.5 mg. in 17 pellets. At the same time the

[8] Supplied as neo-Hombreol by the Roche Organon Company.

[9] Supplied as oreton ointment by the Schering Company.

patient resumed his injections of testosterone propionate, 25 mg. 3 times weekly. Four and a half weeks after the implant he reported a marked sexual stimulation and had masturbated once producing 2½ cc. of secretion. His height and weight had remained stationary. The penis at this time measured 6¼ cm. in length and 8½ cm. in circumference; and the testes were 3 by 1¾ cm. bilaterally. The penis therefore had increased in circumference but only slightly in length since the addition of the implants. A bone age determination at this time was 18 to 19 (chronological age, 32), or an increase of 4 years in 6 years' elapsed time.

Case 6. B.C., (*U4545*) (fig. 9, 9A, 9B), a 17-year-old student was seen at the University of California Clinic in March, 1933. Examination showed him to be 63¾ inches in height with disproportionately long extremities. The genitalia were underdeveloped (length of penis 7 cm., testes the size of small olives and prostate barely palpable). His voice was high pitched, he had no beard and axillary and pubic hair were completely lacking. His weight was 114 lb. and the blood pressure was 95 systolic and 65 diastolic. The B.M.R. was −24%, glucose tolerance curve was a low normal and the sella turcica appeared slightly small. The bone age was 15 to 17 years.

For the first 6 months the patient was given daily injections of gonadotropin.[10] His sexual status as well as his height remained unchanged, but his weight increased to 123 lb. and the B.M.R. to −16%. He was then given 1 grain of desiccated thyroid daily for 13 months, during which time he grew to a height of 66½ inches and a few pubic hairs appeared. However, the sexual status remained otherwise unchanged.

After 5 months without therapy (at the age of 19½ years) he was started on androstine,[11] 6 tablets by mouth and 1 ampule by injection daily. After 10 months of this treatment, he was having erections twice a week and emissions about twice a month, but the genitalia were unchanged in size. At this time his height was 67¾ inches, his weight 132 lb., the length of the penis 7 cm., the testes the size of medium olives and a few wisps of pubic hair were present.

After a brief lapse in therapy, on Nov. 6, 1936, when the patient was almost 21 years old, he was started on testosterone propionate[12] 5 mg. hypodermically 3 times weekly. A definite response occurred and after 5 months the dose was increased to 25 mg. 3 times each week. In May, 1938, the bone age was still 16 to 17 years. In February, 1939, after 2¼ years of this therapy, the patient was having erections each day and emissions about 3 times weekly; so the frequency of the injections was cut to twice weekly. This was continued until November, 1939, when the penis was considered of adult size (length 11½ cm.), and the testes and the prostate were about half normal size. Prostatic secretions were normal but no spermatozoa were seen. The patient was having 0 to 5 erections daily and emissions about twice weekly. His voice was deeper and he was shaving every 2 weeks. The pubic hair had increased and there was moderate growth

[10] Antuitrin-S, Parke, Davis & Co.

[11] Kindly furnished by Ciba Pharmaceutical Products, Inc.

[12] Perandren, kindly furnished by Ciba Pharmaceutical Products, Inc.

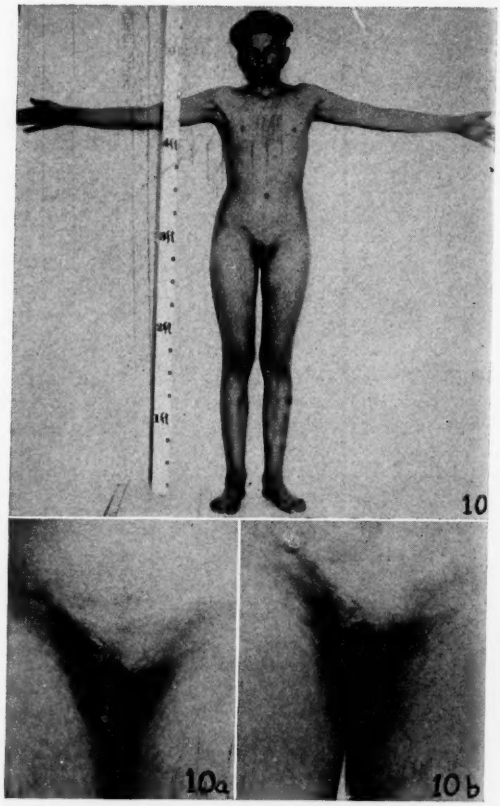

Fig. 10. *Case 7*, primary hypogonadism; age 24, looks younger. Note disproportionately long extremities, feminine contour of thighs, tiny genitalia, sparse pubic and axillary hair. Voice high pitched; upper eyelids show puffy appearance characteristic of eunuchoidism. Fig. 10A. *Case 7*, age 24; before treatment. Operative scar dates back to hernia repair in early childhood. Note tiny penis. Left testicle in lower end of inguinal canal. Fig. 10B. *Case 7*, appearance 1 month after implant of 180.1 mg. of methyl testosterone. Had priapism for 1 week starting 2 days after the implant.

of axillary hair. His weight was 168 lb. (a gain of 36 lb.).

Treatment was then discontinued. A condom specimen after 2 months showed no spermatozoa and at this time the libido diminished and then disappeared. After 4 months without treatment, the patient still was having erections nearly every day, but emissions occurred only every 3 weeks. He had lost 14 lb. (to 154½ lb.). He was more nervous and required more sleep. His beard was growing less vigorously so that he shaved only every 3 or 4 weeks. The penis was smaller, measuring 9½ cm. in length and 9¼ cm. in circumference. Each testis measured 4 by 2 cm. The prostate could barely be felt. Height was now 70½ inches and the blood pressure was 110 systolic and 60 diastolic. The B.M.R. was −13% and the bone age had increased to 18 to 20 years (chronological age 24). Urinary androgens were tested in a 3-day sample and the excretion was 5 I.U. per day (normal 25 to 50).

At this time (March 21, 1940) an implant of methyl testosterone was given totalling 109.6 mg. distributed in 20 pellets. A definite effect was apparent 1 week later when erections had increased to 3 to 5 daily and the patient began to have fairly frequent nocturnal emissions. After 8 weeks he was still having 2 erections daily and emissions every second night. His penis now measured 11½ cm. in length (a gain of 2 cm.) with a circumference of 10½ cm. The testes were unchanged. Another implant was then given totalling 138.3 mg. of methyl testosterone distributed in 16 pellets.

Case 7. R.C., (*U57397*) (fig. 10, 10A, 10B), a 24-year-old student was first seen in the University of California Clinic on April 12, 1940, his chief complaint being "lack of development." An identical twin brother had matured physically but was mentally retarded. The patient's development had paralleled that of his brother until the age of 12, but had progressed no further. The left testis was undescended but had come down once previously during some treatment with an anterior pituitary preparation which had also caused the patient to shave infrequently for a limited time. He was always cold and his general strength was below the average. His height was still increasing by about ½ inch a year. He had never had any libido, though occasional erections had occurred as well as a few nocturnal orgasms without secretion. In the preceding 5 months he had had several nocturnal syncopal attacks with sweating and pallor followed by nausea and vomiting. The patient had finished high school but had been unable to obtain employment because of his youthful appearance and high pitched voice. At this time he was attending a trade school and doing housework to support himself.

On examination he was found to be slender and to look younger than his age. His height was 66¾ inches and his weight 129 lb., with disproportionately long extremities. His eyelids were puffy and the skin was dry, wrinkled and of a mottled, fawn color. There was a moderate amount of axillary hair but the pubic hair was scant. The penis was small, measuring 5 cm. in length and 5½ cm. in circumference. The left testis was undescended, both were the size of small olive pits. Prostatic tissue was barely palpable. Laboratory studies showed: B.M.R., −5%; plasma cholesterol, 175 mg.%; glucose tolerance curve, normal; no urinary creatin; bone age, 16 to 17 years (chronological age, 24); urinary androgens in a 3-day specimen, 5 I.U. (normal 25 to 50).

On April 17, 1940, the patient was implanted with 19 pellets of methyl testosterone totalling 180.1 mg. Two days later he developed priapism which lasted for 1 week. He then had 5 to 6 erections daily, until about 1 week before his last visit 5½ weeks after the implant. Nocturnal emissions had occurred 2 to 3 times a week. The patient stated he felt stronger. His weight and height were unchanged, but the penis was larger, measuring 7 cm. in length and 8 cm. in circumference. The testes were slightly larger.

DISCUSSION

In the above cases an implant of testosterone propionate was used only once, namely in *case 1*. Because of the infection that occurred, methyl testosterone was chosen for all subsequent implants. However, in spite of the infection and probable loss of some of the pellets, the testosterone propionate caused a decided clinical response. The subsequent doses of methyl testosterone in the same patient caused continued improvement and the duration of effect was approximately the same, but the results were not quite as dramatic.

Case 2 was not that of a primary eunuchoid but of one who developed hypogonadism coincidentally with hyperthyroidism. The latter was changed to hypothyroidism by a subtotal thyroidectomy, and this was in turn corrected by treatment with desiccated thyroid. All this fluctuation in thyroid function had no effect whatsoever on the patient's hypogonadism. The initial dose of 125 mg. of methyl testosterone caused some improvement but was not sufficient to restore potency. However, the second dose of 98.5 mg. given 5 weeks later had the desired effect. It was also interesting to note that as the patient's sexual function improved he needed less thyroid to control his hypothyroidism.

In cases 3 and 4 implants were used as continuation therapy after prolonged treatment with testosterone propionate injections. In these instances improvement was maintained. *Case 3* went 9 weeks without definite diminution of libido, but then noticed a change coincident with a pyelitis. *Case 4* noted an increased level of libido and sexual function after the implant and did not experience a diminution, until after 7- and 8-week intervals.

Case 5 had also had injections of testosterone propionate for a long period of time. His genitalia were the smallest of any in our group. As his condition seemed to be stationary as regards further growth of genitalia, the implants were given in addition to the usual testosterone injections. A definite increase in the size of the penis resulted.

Case 6 had had prolonged therapy with testosterone propionate so that his genitalia had attained adult status. However, treatment had been discontinued for 4 months, and after 2 months definite diminution in genital function and size had occurred. After the implant there was a restoration of function and increase in size.

Case 7 presented a striking deficiency and had not had previous testosterone therapy. The preparation of the larger pellets made possible a greater initial dosage in his case (180.1 mg.). The result of priapism for 1 week would seem to indicate that the dosage was too large in this instance. Cases with marked deficiency and without previous testosterone therapy seem to show a more intense initial response to implantation.

The obvious effects of treatment by implant are similar to those following injections of male hormone.

Increase in size of genitalia and increase in sexual function have resulted. A definite increase in size of the prostate occurred under therapy with both injections and implants (*case 1, 3, 4* and *5*). *Case 2* in whom the eunuchoidism developed at the age of 42, had a very small prostate, apparently due to lack of male sex hormone. This finding is difficult to reconcile with the testosterone treatment of prostatic hypertrophy.

Gain in weight was a frequent result of therapy, being marked in cases 2, 3, 4, 5 and 6. An increase in general strength was universal. The beard growth became somewhat heavier as a result of treatment, but never approached normal except in *case 2*. There was never any definite effect on blood pressure, all of the patients having low normal levels.

Cases 1 and 5 had fairly low basal metabolic rates, but only one of these (*case 5*) was raised to normal by treatment. Retarded bone age is a characteristic finding in the pre-adolescent eunuchoids and this showed advancement under therapy in all the cases tested (1, 3, 4, 5 and 6).

A study of androgen excretion was not helpful. The amount was always diminished or absent before treatment and there was occasionally some increase after therapy, but in *case 2* the opposite effect was noted. The most marked increase was in *case 4* after therapy with the equine gonadotropic hormone (0 to 21 U daily), but the excretion diminished to 5 U daily following later treatment with testosterone. From our observations it would seem that androgen determinations are of little value in checking the improvement from testosterone therapy, nor are they necessary even for diagnostic purposes. In view of this limited clinical usefulness and the elaborate time-consuming and expensive laboratory procedure necessary for accurate determination, quantitative androgen assays are not recommended in clinical practice.

In cases 3, 4 and 6 it was possible to compare the effects of the implantation of methyl testosterone pellets with the injection of testosterone propionate in oil. Satisfactory results had been obtained with 25 mg. of the testosterone propionate injected 3 times weekly. In these instances the patients showed no subjective or objective diminution of effect on the pellet regime. In *case 3* the first implant was effective for 9 weeks and the second for 8 weeks. Thus, over a period of 17 weeks, 206 mg. of methyl testosterone in pellet form was adequate substitution for 1275 mg. of testosterone propionate in oil, which would have been administered hypodermically in the same period of time. In *case 4* the first implant was effective for 7 weeks, the second for 8 weeks. In this period of 15 weeks, 213 mg. of methyl testosterone pellets proved as effective as 1125 mg. of testosterone propionate in oil which would otherwise have been used. Similarly, in *case 6* the first implant of 109.6 mg. was effective for 8 weeks, and thus replaced 600 mg. of testosterone propionate in oil. Thus, in these 3 cases 528 mg. implanted equalled 3000 mg. parenterally in oil.

The duration of effectiveness with a total dose of approximately 100 mg. of methyl testosterone varied from 35 to 70 days, with an average of 49 days, or 7 weeks. The only figures available at this time on the duration of effect following the larger doses of 140 to 180 mg. are two instances in cases 5 and 7. It was anticipated that the effective period would be prolonged, but it was not the case in these instances. When an implant has been 'used up,' no pellets can be felt at the site and there have been no indurations or other unpleasant local symptoms.

SUMMARY

Seven typical cases of eunuchoidism are presented —6 of the preadolescent type and 1 in which the onset seemed related to hyperthyroidism. Treatment was by implanting pellets of crystalline methyl testosterone and/or crystalline testosterone propionate. Total dosage of each implant early in the work varied between 83 and 125 mg. compressed into pellets averaging 5 to 6 mg. each. Later larger pellets were prepared so that doses of 140 to 180 mg. could be given. This was the only type of treatment in three of the cases but in three of the remainder it was used as continuation therapy after injections in oil, in order to compare the effectiveness of the two methods of treatment in the same individual. In the remaining case, pellets were given in addition to continued injections in oil to determine the effect of additional dosage. The duration of effectiveness with the smaller dosage averaged 7 weeks. Testosterone propionate pellets seemed somewhat more potent clinically, but methyl testosterone was easier to prepare and safer to administer. The absorption from each pellet of methyl testosterone was approximately 0.1 mg. to 0.17 mg. per day and the effective clinical dosage was found to vary between 2 and 3 mg. per day.

The method of preparing these pellets is described in detail and the technical difficulties are discussed. The high melting point of methyl testosterone pellets permits sterilization in the pressure autoclave, thus materially reducing the possibility of contamination.

This experience indicates that the uniform continuous absorption from such pellets is more efficient than injections of the hormone in oil so that approximately one-fifth of the dosage is required to obtain similar results. The eventual cost of continuous treatment should therefore be less and the interval of about 7 weeks between implantations is a decided improvement over injections 2 to 7 times weekly.

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STILBESTROL

A CLINICAL STUDY IN ESTROGENIC THERAPY[1]

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AN ESTROGENIC PREPARATION that can be administered orally has long been desired. The wish seems to have been fulfilled by the discovery of stilbestrol. Favorable reports of the estrogenic efficiency of this compound are numerous, but a variety of opinions concerning its toxicity have been expressed. During the past year my associates[2] have collaborated with me to observe the effects of stilbestrol administered to 250 patients. We have been interested to test the efficiency, toxicity, optimum dosage and indication for the use of stilbestrol.[3]

In order to avoid prejudice each observer selected his own cases, chose the dosage and recorded his results. All other complaints and symptoms of the patients as well as the estrogenic deficiency have been considered and treated concurrently with the stilbestrol therapy. Only the patients who have returned for observation are included in this report, though it might be assumed that many of those who received the medication were sufficiently relieved of their symptoms to feel it was not necessary to return. As far as possible the results are presented in the following tables. Some require individual consideration.

The discovery of stilbestrol and animal experimentation with the compound have been adequately presented in current literature of the last two years. It will not be repeated here.

The criteria for judging the effects of stilbestrol have been limited to clinical observations and statements of the patients. While subjective symptoms are not as dependable as objective, it has been necessary to utilize both because many of the symptoms of apparent estrogenic deficiency are subjective. The predominance of the menopause cases in this series emphasizes the necessity of relying on subjective symptoms.

Laboratory procedures, especially vaginal smears, have been instituted whenever indicated. Since our results resemble those reported by Shorr[4] further details are not reported. So few toxic manifestations were encountered that relatively few liver function tests were made.

TOXICITY

Experience with toxicity of stilbestrol varies widely. I have talked with four gynecologists who said that every time they used the preparation the patient vomited. They refused further trial. Our experience has been different (table 1). The dosage has varied from 0.1 mg. to 30 mg. daily. The toxicity is apparently not related to the amount of the drug.

TABLE 1

Total patients treated	250	
No toxic manifestation	228	91+%
Definite toxic manifestation	9	3.6% } 8.8%
Doubtful toxic manifestation	13	5.2% }

In order to explain the significance of doubtful toxic manifestations, abbreviated case reports are presented.

Case 1. Patient, aged 57, complained of many neurotic symptoms, among which were hot flushes and sweats. These might be attributed to the menopause or to a purely nervous origin, probably the latter. She claimed to be sensitive to practically all medicine. She took one tablet and refused to take any more, though there were no specific complaints of toxicity.

Case 2. The original complaint included a bizarre symptomatology with many nervous manifestations and gastrointestinal disturbances. After taking the stilbestrol she complained of slight dizziness, but she continued to take the medication and the symptoms disappeared in a few days.

Case 3. A report by letter stated that there was a little nausea the first few days after taking the medicine. She persisted and complained of no more toxic symptoms.

Case 4. A patient, aged 33, treated for artificial menopause complained of epigastric distress before treatment was begun. She had a marked psychoneurosis with a multiplicity of complaints and hot flushes. The epigastric distress continued. She thought it was a little worse after

[1] Read before the Twenty-fourth annual meeting of the Association for the Study of Internal Secretions, New York City, 1940.

[2] From the Division of Gynecology and Obstetrics, Henry Ford Hospital, including the observations of Doctors M. Smeltzer, M. R. White, H. L. Stewart, R. F. Stover and C. P. Hodgkinson.

[3] The stilbestrol used has been supplied by the courtesy of E. R. Squibb & Sons and Parke, Davis & Company.

[4] SHORR, E., F. H. ROBINSON AND G. N. PAPANICOLAOU, J.A.M.A., 113:2312. 1939.

medication and stopped after two weeks treatment but the menopausal symptoms were relieved temporarily.

Case 5. A patient having nervous manifestations associated with menopause was relieved and continued to take the stilbestrol over a period of 3 months but at rare intervals complained of slight nausea. There were many more probable reasons for the nausea.

Case 6. A patient with menopause and many nervous manifestations complained of slight nausea but continued to take the stilbestrol. The nausea soon disappeared.

Case 7, 8. These patients had slight nausea part of the time during medication but continued to take the stilbestrol. The nausea soon subsided.

Case 9. One patient insisted that she could not take the pills because they made her "all shuddery." She said, "I shivered and trembled so much that I fell down and broke my arm." There were no gastrointestinal symptoms. She stated that she is sensitive to many medicines—"It took them 4 years to get me up to ¼ grain of thyroid."

Case 10. One doubtful case had two attacks of vomiting during the month while taking stilbestrol. She continued to take it and had no further disturbance.

Case 11. The patient experienced dizziness as soon as she began to take stilbestrol. The same experience recurred when it was repeated. She stated, however, that these spells of dizziness had been associated with low blood pressure over a period of several years and thought that the dizziness was aggravated by taking the medicine.

Case 12. This patient, who took stilbestrol for nearly a year, had a severe gall bladder attack with nausea and vomiting during the fifth month of medication. She was out of reach of advice from us and continued to take the stilbestrol during the gall bladder attack. There were no toxic symptoms that could be attributed to the stilbestrol before or after this attack. It seems doubtful that the medication had anything to do with the nausea or vomiting.

Case 13. A patient under treatment in the Gastrointestinal Department complained of some abdominal distress during the treatment with stilbestrol. The symptoms were no different from those she had previously experienced.

The arbitrary assignment of these cases to the classification of toxic and doubtful toxic is debatable. Critical analysis discloses evidence for and against the symptoms being due to a toxic reaction to stilbestrol. In my opinion, at least half of the 22 cases were not toxic, but, in view of other reports of high incidence of toxicity, it seems best to consider them toxic until proved otherwise. All toxic symptoms disappeared promptly when stilbestrol was discontinued.

The largest group of cases studied exhibited menopausal symptoms (table 2).

TABLE 2. MENOPAUSE

Total menopause cases	124	
No. completely relieved	93	75%
No. partially relieved	21	17−%
No. not relieved	10	8+%

Pre- and postmenopausal states were included in this series of 124. The time relation to the last menstruation ranged from regular cycles still maintained to an interval of 25 years. The optimum dose was 1 mg. daily. A few required as much as 5 mg. daily while others were relieved by 0.1 mg.

The vagaries of the menopause produce complicated pictures suggesting varied interpretations. It may be noted that although this group confirms only one-half the whole series, nearly all the toxic manifestations appeared in the menopausal patients. Further analysis would lead to a prolonged discussion.

SENILE ATROPHY

The term senile atrophy is intentionally ambiguous to include a variety of regressive changes in the vagina and external genitals ranging from dryness of the vagina to kraurosis vulvae (table 3).

TABLE 3. SENILE ATROPHY

Total cases	52	
Complete relief	38	73+%
Improved	13	25%
No relief	1	2−%

Treatment of senile atrophy was highly satisfactory for two reasons: *a*), the chief symptom being objective permitted a reliable estimate of the effect of therapy, *b*), the results were gratifying to the patient and physician. The lesser degrees of regression responded promptly and completely to therapy. The subjective relief experienced, if recorded, would rival the enthusiasm expressed in testimonials published in behalf of patent medicines used to restore lost manhood. Dyspareunia disappeared, marital relations, abandoned for years, were resumed and the attending nervous phenomena were transformed almost miraculously. If regression had advanced to kraurosis, little improvement resulted from therapy, though one case improved temporarily. The dosage required in this group varied from 1 to 10 mg. daily. No benefit was derived from higher doses.

PRURITUS

Among the 15 cases of pruritus treated, 5 were relieved, 8 improved and 2 showed no change. Pruritus is not an entity. It was associated with the menopause, senile atrophy and general metabolic disturbances.

HYPERTENSION

Several instances of arterial hypertension were noted, particularly in the menopause group. It is noteworthy that during therapy the level of blood pressure was not materially altered. Even when the menopausal symptoms were completely relieved the blood pressure was not changed.

WITHDRAWAL BLEEDING

Bleeding occurred frequently after cessation of stilbestrol therapy. The interval between the last dose and bleeding varied from 1 to 14 days. The amount varied from spotting to a heavy flow. The duration of the flow varied from a few hours to several days. Frequently the patient stated, "It was like a normal menstruation." The data submitted do not justify prediction for the individual beyond the warning that she is likely to flow after she stops the medication.

AMENORRHEA

Primary amenorrhea rarely yields to any form of therapy. No appreciable results were obtained in 3 patients. Secondary amenorrhea, generally more amenable to treatment, responded favorably in 11 patients. One of these is worthy of special comment regarding dosage and decreased sensitivity.

A patient, aged 41, was much concerned about sterility. She menstruated scantily and at long intervals for a period of a few years. Other medication was tried including thyroid therapy, a course of theelin and later equine gonadotropic hormone. In each of these trials she experienced temporary improvement in the amount of menstruation and shortening of the interval. After a few months with each medication, the uterus apparently lost its sensitivity and the menstrual flow diminished in amount and the intervals became farther apart. Stilbestrol was used with a favorable response as withdrawal bleeding occurred 10 times during the year. Starting with 1 mg. daily the dose was increased to 10 mg. as the sensitivity seemed to diminish. In spite of this increase at the end of a year she failed to respond to the large doses of stilbestrol. This seemed to be a case of diminished sensitivity.

MENORRHAGIA AND METRORRHAGIA

All functional bleeding cannot be attributed to a single cause. One theoretic explanation, that continuous bleeding may occur when estrogens are maintained at nearly a constant level, offers a basis for stilbestrol therapy. If stilbestrol is administered in sufficient quantity for a brief period, cyclic variations may be simulated. Withdrawal bleeding occurs with the reduction of estrogenic stimulation. The following patient was treated on that theoretic basis with apparent success.

A woman, aged 28, first seen in 1936 complained of profuse and prolonged menstruation (15 to 44 days). Hyperplasia of the endometrium was discovered by currettement May 25, 1937. Treatment including thyroid, calcium and chorionic gonadotropic hormone, failed to reduce the excessive bleeding. Treatment with stilbestrol was started August 17, 1939. She had been flowing constantly for 24 days. Five mg. of stilbestrol were given daily for 10 days. The flowing stopped 9 days later. After a free interval of 20 days she flowed 10 days. At the cessation of this flow 10 mg. of stilbestrol were given daily for 6 days. Flow began 4 days after last dose and lasted 9 days. One day later 10 mg. of stilbestrol were given daily for 11 days. Flow began 6 days later and lasted 6 days. Seven days later 5 mg. of stilbestrol were given daily for 12 days. Flow began 3 days after the end of this treatment and lasted 9 days. Stilbestrol, 5 mg. daily, was started 16 days after the last flow stopped and continued 10 days. Flow started 3 days later and lasted 7 days. Stilbestrol, 5 mg. daily, was started 18 days after last flow. Flow started 4 days after last dose and lasted 7 days. No treatment was given during the next interval of 30 days, then she flowed 9 days. When the succeeding flow was prolonged to 12 days, stilbestrol, 5 mg. was started. She stopped flowing in 2 days. She is still under observation.

Among the 7 cases treated for excessive bleeding, 1 became worse during treatment, 2 were improved and 4 satisfactorily controlled. As a corollary to the control of functional bleeding and withdrawal bleeding, menstruation was delayed in 2 patients by continuing the administration of stilbestrol for 1 week after the menstruation was due. Flow began 5 days after cessation of treatment, i.e., the flow was 12 days later.

BREAST CHANGES

Enlargement, tenderness, tingling or pigmentation of the breasts were frequently noted. No consistent relation of the symptoms to the dosage, age, or condition of the patient were noted. Inhibition of engorgement of the breast was studied in 52 cases and will be reported later.

SUMMARY

Stilbestrol possesses estrogenic activity similar to estrone. It has the advantage of being effective when administered orally and of being cheap.

Toxicity appears to be an individual idiosyncrasy.

The optimum dose for most conditions treated is 1 mg.

Decreased sensitivity may follow long continued administration.

Indications for the use of stilbestrol, as well as its limitations, are evolving through numerous clinical observations and reports.

STILBESTROL

A CLINICAL STUDY IN ESTROGENIC THERAPY

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IN COMPARATIVELY RECENT YEARS the benefits derived from the use of estrogenic substances have been widely accepted. Many articles have been written in lay publications as well as medical periodicals eulogizing the entrance of these hormones into the armentarium of therapeutics.

In spite of the known effect of these preparations and in spite of the many patients who have been benefited by their use, there are many more persons who have not received these needed hormones. The chief reasons which have deprived these deserving individuals of necessary treatment are the expense associated with their procurement and by no means a minor consideration, the necessity of repeated hypodermic injections for their effective use.

In 1938, Dodds, Goldberg, Lawson and Robinson (1) announced the synthesis of a new agent, diethyl stilbestrol, which has estrogenic properties. It was found to be almost as potent by oral as by parenteral administration and more active than natural estrogens.

This new preparation seemed most promising for wide-spread use because of its potency and because it met the two prime objections to the natural estrogens mentioned above.

Subsequent publications concerning the use of stilbestrol in human subjects have been consistent in establishing this product as an effective estrogenic preparation both orally and hypodermically. There have been varying reports as to the toxic reactions which accompany its use. Bishop, Boycott and Zuckerman (2) reported nausea and vomiting in three of 46 patients receiving stilbestrol. Winterton and MacGregor (3) reported that some of the subjects in their series of 51 patients experienced slight nausea, but that the drug was poorly tolerated in only one instance. Other investigators (4, 5) have reported a much higher percentage of undesirable reactions as nausea, vomiting, vertigo, headache and abdominal pain and some (6) go so far as to condemn the use of stilbestrol because of extremely unpleasant by-effects.

It is not within the province of this paper to review the literature on the subject in detail. During the past year, stilbestrol has been administered to 64 patients. These women have presented a variety of diagnoses and symptoms. Treatment was administered by both oral and intramuscular means. Dosage varied from 0.2 to 40.0 mg. daily. Many of the patients were followed with basal metabolism, blood pressure, pulse, blood counts, vaginal smears and endometrial biopsy. It is not possible to draw broad conclusions from so small a series of patients as the present one. However, we are presenting here our observations on the individual groups classified by diagnosis.

Various toxic symptoms have been noted with the use of stilbestrol. The most common have been nausea and vomiting, but other symptoms such as headaches, vertigo, tingling sensations, numbness of extremities and skin rashes were sometimes noted.

We considered the tolerance of stilbestrol as "good" when the patient manifested none of the toxic symptoms mentioned. Tolerance was "fair" when she complained of some of the toxic symptoms but was able to continue therapy. Tolerance was considered "poor" when the toxic symptoms were so severe that further therapy was impossible.

In general the smaller dosage was better tolerated. The optimum dosage from the point of view of tolerance of medication and procurement of desired effect seemed to be between one and two milligrams daily by mouth.

Three times we noted a reversal of tolerance. Each time the patient, who had previously taken the medication well and had obtained an excellent response, was given a rest period. On reinstitution of treatment, violent nausea and vomiting prohibited continuation of treatment. More frequently, however, such reactions to return to treatment were not noted. Usually the same type of response was observed with a second course of medication as with the first.

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We have been impressed, generally, with the fact that the better the tolerance to stilbestrol, the better the response we might expect in the patient.

PHYSIOLOGICAL MENOPAUSE (15 CASES)

		Response
Good tolerance	12	Good 11 Poor 1
Fair tolerance	2	Good 1 Fair 1
Poor tolerance	1	

This group of patients presented the typical menopause syndrome. Hot or cold flushes, nervousness, vague aches and pains, myalgia, emotional instability, etc., were the presenting complaints. In natural menopause the age limits were from 38 to 60 years. The duration of symptoms was extensive. Some of the patients were classified as "early" menopause even though a degree of menstrual flow still persisted. At the other extreme was a women 60 years old who had experienced a severe menopause syndrome for over 10 years. Dosage varied from 1 mg. by mouth to 5 mg. intramuscularly. Interval of treatment extended from daily to once a week. Duration of treatment was from five days to one year.

First we will consider those women in whom tolerance was good. Eleven of 12 of these women demonstrated marked improvement. Usually improvement was noted before a week of therapy was completed. There was no definite relationship between dosage and degree of response. The usual effective dose was 1 mg. once or twice a day by mouth or 5 mg. intramuscularly once or twice a week.

One patient, who tolerated the treatment well, warrants discussion. Although relieved of the symptom complex, 10 days after onset of treatment with 1 mg. daily by mouth, vaginal spotting was noted. Treatment was discontinued. Four days later severe bleeding occurred, requiring curettage. The pathological diagnosis was endometrial hyperplasia. This may be considered as an 'estrin deprivation' bleeding.

Only one patient in physiological menopause, who tolerated treatment well, showed no response to stilbestrol. This woman of 47, responded well to natural estrogens but neither 2.5 mg. stilbestrol, intramuscularly, at weekly intervals nor 1 mg. daily for 2 weeks, elicited any desired effect.

One patient of 53 years, presented a picture of unusually severe menopause syndrome. There had been no menstrual flow for over one year. A small subserous myoma was present. One milligram of stilbestrol was taken twice a day for 3 weeks. The subjective response was remarkable. Endometrial biopsies before and after treatment showed a marked change from a quiescent endometrium to a typical Swiss cheese hyperplasia. The subserous myoma increased in size 4 times. With discontinuance of medication scant vaginal bleeding occurred.

One patient, 39 years old, presented an early menopause syndrome. Treatment consisted of 1 mg. stilbestrol daily for 6 months. Tolerance was good. Treatment was discontinued for 12 days. When begun again, a complete reversal of tolerance was noted. Nausea and vomiting, numbness of extremities, vertigo, headache and tingling of the fingers prevented either oral or intramuscular administration. This reversal of from good to poor tolerance has been noted several times.

Of two patients in this group, who tolerated treatment only fairly well, one responded well and one showed only a fair response.

Only one patient in physiological menopause tolerated stilbestrol so poorly that treatment had to be discontinued.

POST RADIATION MENOPAUSE

There were 3 patients in this group. One woman, 41 years old, was in menopause following 1800 mg.hr. of radium for abnormal bleeding associated with a myomatous uterus. One milligram of stilbestrol was given twice a day by mouth. The flushes began to lessen on the fourth day of treatment and disappeared completely after the ninth day. Insomnia was gone by the sixth day. The dosage was reduced to 1 mg. daily for 2 more weeks and then therapy was discontinued. Four weeks later the symptom complex returned, and again was entirely relieved by the administration of stilbestrol.

The second patient in this group is of particular interest because of her variation in tolerance to the medication. This woman of 46, had a severe menopause syndrome since radium had been given 4 years before for functional bleeding. Therapy during this time included thyroid and estrogens with variable response. Stilbestrol was given orally in dosages of 5 to 10 mg. 3 to 4 times daily for 2 weeks. A marked change was encountered. She noticed a distinct "lift" and "life was worth living." The dosage was reduced to 1 mg. twice a day with continued improvement. She noticed a "fullness" in the genital areas, the vaginal membrane became succulent, and a smear revealed disappearance of the atrophic picture previously encountered. Stilbestrol was discontinued for 3 months with a return of the entire symptom complex. Estrin was administered, 10,000 U weekly for another 2 months with very poor response, so stilbestrol was again begun. One milligram stilbestrol twice a day produced retrogression of the symptoms, but now the patient tolerated medication poorly. Nausea, at times severe, became a constant symptom. However, improvement due to the therapy was sufficient for the

patient to be willing to tolerate the discomfort of the side actions of the drug. Later, thyroid was combined with stilbestrol with an even greater subjective improvement. At no time has there been any variation in pulse, blood pressure or basal metabolism which could be attributed to stilbestrol. This patient has taken as much as 40 mg. of stilbestrol daily. No change in reaction was noted with plain or enteric coated tablets.

The third woman in this series reacted very badly with nausea, vertigo and anorexia. Therapy was discontinued before any conclusion could be drawn.

POST-OPERATIVE MENOPAUSE (13 CASES)

		Response
Good tolerance	8	Good 7 Poor 1
Fair tolerance	5	Good 2 Fair 2 Poor 1
Poor tolerance	0	

The symptom complex noted among these patients was the typical one noted among menopause patients. Flushes, lassitude, headache and insomnia were frequent symptoms. Pruritis and sexual frigidity were noted less frequently.

Dosage in the 8 patients who tolerated the medication well, varied from 1 mg. daily by mouth to 5 mg. intramuscularly at weekly intervals. The average age was 40 years. Previous medication included use of bromides and sterile water hypodermics given to rule out psychic response. In 7 of these 8 patients, the response to medication was excellent. Complete relief of symptoms was usually noted within one week. No relation was observed between dose of medication (provided at least 1 mg. was given daily) and the subjective response. One patient who tolerated the medication well showed no response.

Two patients tolerated medication only fairly well, but responded well. Both these women received 5 mg. intramuscularly at weekly intervals. Nausea was the symptom of intolerance in both cases but treatment was continued because of the excellent subjective response.

Two patients tolerated medication only fairly well and responded only fairly well subjectively. Both these women were treated with larger doses. One received 1 mg. orally 3 times a day for 2½ months and the other received 1 mg. daily for 10 days followed by 3 to 5 mg., intramuscularly at weekly intervals for 3 weeks. Nausea and vomiting were the undesirable symptoms. In each of these 2 patients, the results were fair, only a partial relief of symptoms being noted.

One patient tolerated treatment fairly well, but responded poorly. She was given from 1 mg. daily by mouth to 5 mg. intramuscularly at various times for several months. At no time did this patient exhibit a desired response to the medication, although she repeatedly responded well to estrone and estradiol. At one stage of observation this patient bled from the uterus 5 days after a course of 50 mg. of stilbestrol taken by mouth during 2 weeks. An endometrial biopsy demonstrated a marked proliferative endometrium with no evidence of secretory phase. This is one of few patients in whom absolutely no subjective response to medication was noted although an anatomic response was noted.

Generally in this series the patients who tolerated medication well (eight) obtained excellent results. Those who tolerated medication only fairly well (five) responded in a varied manner; two responded well, two fairly and one not at all.

DYSMENORRHEA (5 CASES)

Two patients reacted so badly with nausea and vomiting that no response could be deduced.

One patient, 30 years old, married, complained of severe dysmenorrhea, dyspareunia, severe premenstrual tension characterized by an unstable emotional state, "drawing" pain in legs and thighs, headache, backache. Pelvic examination revealed a general hypoplasia of the genital tract with small labia, small vagina, short anterior vaginal wall, tiny cervix and retrodisplaced uterus. Intramuscular stilbestrol caused severe nausea for 48 hours. Oral therapy was well tolerated. One milligram of stilbestrol was given twice daily. After 10 days the patient noted enlargement of breasts and increase in vaginal secretion. Two days after stilbestrol was discontinued, a menstrual period began. This period was free of the usual premenstrual tension but the pain was even worse than usual. Stilbestrol was continued, 1 mg. B.D. for 4 weeks. No flow had occurred to the 28th day, so stilbestrol was discontinued. Five days later a normal flow began. The premenstrual tension was not noted; neither were cramps present, although headache and backache persisted. Premenstrual examination revealed a much softer vaginal membrane. Examination with two fingers was possible. Dyspareunia was almost entirely eliminated.

Another patient, white, female, 23 years old, not married, on examination revealed normal pelvic organs. One milligram of stilbestrol was given every 3 days for 5 doses beginning with the onset of a period. The subsequent period was free and painless. Therapy was discontinued and the next period presented the usual dysmenorrhea.

A third dysmenorrhea patient, who tolerated treatment well, was white, 23 years old and married. This woman presented a complex of severe dysmenor-

rhea, always delayed menstrual periods, from 3 to 10 days, and an infantile uterus with normal external genitalia. One milligram of stilbestrol was given twice daily for one month. The following period was at 28 days and free of pain. The uterus was not larger. With discontinuance of stilbestrol, the menses became later and later, and dysmenorrhea became progressively more severe. Before stilbestrol was reinstituted, the patient became pregnant.

VAGINITIS, VULVITIS, PRURITIS

An elderly woman, 68 years old, with typical leukoplakic vulvitis and pruritis, was given 1 mg. of stilbestrol daily by mouth. Treatment was well tolerated. After 10 days, the pruritis disappeared, the vaginal membrane became softer and the patient was entirely comfortable even though the leukoplakia persisted.

One woman, 64 years old, with senile vaginitis and vulvitis, was given 1 mg. of stilbestrol intramuscularly every 4 days. After 2 treatments the associated pruritis abated and the vaginal membrane was less red. Therapy was well tolerated. This patient is still under treatment.

A young woman, 28 years old, with an atrophic vaginitis, a dry, thin, cracked membrane, was given 5 mg. of stilbestrol intramuscularly at weekly intervals. After 3 injections a striking improvement was noted. Treatment is still in progress.

Two young women, 25 and 28 years of age, with non-specific pruritis vulvae were given 1 mg. of stilbestrol daily by mouth. In one case, after 12 days, the pruritis ceased completely. When treatment was stopped, the itching recurred. However, when stilbestrol was prescribed again, it was not tolerated due to nausea and vomiting. The second case of non-specific pruritis continued without improvement after one week of 1 mg. of stilbestrol daily. The duration of treatment was really not sufficient to warrant a conclusion.

OLIGOMENORRHEA (3 CASES)

Three patients, 29, 31 and 33 years old, presented a complex of secondary oligomenorrhea, secondary sterility and unusually small uterus. These women were given 1 to 5 mg. of stilbestrol by mouth at daily intervals. The medication was not tolerated in any of these cases. Nausea, vomiting and abdominal pain were the symptoms of intolerance. No conclusions could be drawn.

The following group of 8 patients all exhibited a fairly characteristic complex of amenorrhea with genital hypoplasia.

GENITAL HYPOPLASIA (8 CASES)

		Response
Good tolerance	7	Good 4 Poor 3
Fair tolerance	1	Good 1
Poor tolerance	0	

Three patients aged 27, 15 and 37 years, respectively, were treated for 35 to 60 days. Dosage was 0.2 mg., 5 mg., orally, and 5 mg., intramuscularly, respectively. No changes were noticed in primary or secondary sex characteristics in any one of these 3 patients.

In four patients, aged 17, 20, 24 and 39 years, treatment was well tolerated in all instances. The first patient, a 17-year-old negress, presented a secondary amenorrhea with under-development of internal genitalia and headache. The uterus was a scant 2 inches deep. Endometrial biopsy revealed no tissue which could be diagnosed. One milligram stilbestrol was given daily for 17 days. The uterus was then 2½ inches in depth and endometrial biopsy revealed normal proliferative endometrium. Following subsequent therapy with anterior pituitary extract, an endometrial biopsy showed an early secretory endometrium, and 14 days later there was a menstrual flow. Subsequent menstrual periods occurred at intervals of 49 and 30 days without additional therapy.

A second case, a 20-year-old, white female, with a secondary amenorrhea, received 5 mg. of stilbestrol at weekly intervals for 2 months. A menstrual flow was noted after 6 injections. Two periods followed without further treatment.

A third case, a 24-year-old, white female, received 1 mg. of stilbestrol daily for 2 months. This patient had a primary amenorrhea with total absence of primary and secondary sex development. Previous therapy with natural estrogens resulted in improvement. With stilbestrol a decided increment in rate of development of corpus, cervix and breast was noted. Two periods of bleeding were experienced after cessation of therapy.

The fourth case, a 39-year-old white female with a primary hypogonadism, was treated with 1 mg. of stilbestrol every other day, intermittently, for 1 year. A brilliant response was experienced with growth of primary and secondary organs. Estrin deprivation bleeding occurred consistently each time within 1 week after therapy was discontinued.

One patient, 29 years old, with primary hypogonadism, was given 1 mg. of stilbestrol, orally, every other day for 8 months. Tolerance was fair with frequent nausea but no vomiting. Growth of primary and secondary sex organs was noted. Psychic response

was excellent. Estrin deprivation bleeding occurred consistently by temporarily discontinuing treatment.

LACTATION (7 CASES)

Five milligrams of stilbestrol was given intramuscularly in one injection. It is very difficult to evaluate the efficacy of a medication used for the purpose of drying up the breasts.

In one case, 5 mg. of stilbestrol was given to a patient who had had a stillborn child. The drug was administered when the breasts began to engorge. No other therapeutic aid was given, such as icebags, constrictive binder, limit fluids, etc. Within 16 hours the breasts were soft and not tender or painful.

There were 6 patients who had an insufficient amount of milk or other nursing difficulties, associated with emotional states, fissured nipples, etc. Each was given 5 mg. of stilbestrol. No constrictions, etc., were used. In 5 of those cases the breasts remained soft without engorgement and the milk supply decreased to a negligible amount in 3 or 4 days. Four patients tolerated the medication well. The fifth developed moderate nausea and urticaria. The sixth patient complained of severe nausea, vomiting and headache. The breasts continued to engorge and became painful and hard.

The last patient was a 23-year-old, white woman, who developed a mild, acute mastitis on her 7th post partum day. The breasts were elevated, ice caps applied, and the baby continued nursing. This attack subsided in about 4 days. On the 15th day one breast again became engorged and once more the patient was treated with ice bags and elevation. Symptoms subsided in 48 hours. However, when this same breast became reddened and painfully engorged again 2 days later, it was decided to dry up the breasts. Five milligrams of stilbestrol were given and in 6 hours the breasts were no longer painful. The milk supply decreased gradually thereafter.

MISCELLANEOUS (6 CASES)

Missed abortion. One case received 1 mg. 3 times a day for 2 weeks followed by 5 mg. once a day for 1 week. The medication was well tolerated but produced no subjective response of uterine contractions. The product of conception was expelled spontaneously several weeks after stilbestrol was discontinued.

Pituitary headache. A woman, 47 years old, previously responded well to natural estrogens. Five milligrams stilbestrol intramuscularly at weekly intervals elicited none of the relief obtained from previous estrogenic therapy.

Gigantism. A patient diagnosed as hyperanterior lobe pituitarism with poor mammary development was given 5 mg. stilbestrol intramuscularly every 4 days for one month. Although severely nauseated, the patient continued treatment. Good breast development was obtained.

Rheumatoid arthritis. This woman, 40 years old, noted exacerbations of the arthritis at menstrual periods. One milligram of stilbestrol was administered twice daily for 30 days. Two menses were noted, each free of arthritic exacerbation.

Hyperthyroidism. A woman of 38 was given 5 mg. intramuscularly at weekly intervals. Therapy was discontinued because of extreme nausea.

CONCLUSIONS

1. Stilbestrol is a potent agent with estrogenic properties.

2. Stilbestrol is effective and equally tolerated orally and intramuscularly.

3. Generally, dosage of from 1 to 2 mg. of stilbestrol were better tolerated than larger quantities by both oral and intramuscular routes.

4. Of the 64 patients in this series, 69% tolerated the medication well; 17% fairly, and 14% could not tolerate it at all.

5. Toxic symptoms included nausea, vomiting, abdominal pain, anorexia, headache, tingling and numbness, vertigo. No permanent ill effects were noted.

6. Although, generally, the action of stilbestrol is similar to that of natural estrogens, we have observed patients who did not respond to stilbestrol, but who were benefited by estrone and estradiol.

7. It is our opinion that stilbestrol is a valuable medication in the treatment of gynecologic endocrinopathies whose basis is an estrogenic deficiency.

This study was conducted with stilbestrol, supplied by Dr. J. A. Morell of E. R. Squibb & Sons and Dr. D. C. Hines of Eli Lilly & Company.

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CORPUS LUTEUM STUDIES

II. PREGNANDIOL AND ESTROGEN OUTPUT IN THE URINE OF PATIENTS WITH CHRONIC CYSTIC MASTITIS

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THE TERM chronic cystic mastitis has been used for decades to denote a benign lesion of the breast which is neither inflammatory, nor neoplastic. Recent studies indicate that the changes in this disease are associated with endocrine disturbance. Since the condition is no longer considered to be inflammatory the more recent terms suggested include mammary dysplasia, mastopathy, fibrocystic disease and mammary nodosity.

Chronic cystic mastitis or mammary dysplasia comprises three groups of cases. Mild or early cases with painful dense mammary tissue are usually referred to as painful breasts or mastodynia. Cases with more persistent and definite nodularity are referred to as adenosis, shotty breasts or Schimmelbusch disease, after Schimmelbusch who described microscopically the proliferative changes in this condition (1). The third group of cases known as cystic disease is usually unrelated to the other two groups of cases. It is characterized by the development of one or more cysts of appreciable size in women whose breasts have been previously normal.

In painful breasts, usually cyclic women in their thirties are affected. Childless women or women who have not borne children recently are in the majority and among married women sterility is a frequent complaint. Pain, tenderness, swelling or enlargement of the breast are leading symptoms. On examination the pain and tenderness are found in mammary tissue of increased density which is elevated and granular to palpation. Discrete nodules may or may not be found in this condition. Excised tissues on microscopic study show defective lobule formation. The mammary tubules have enlarged end-buds with occasional small lobules and are surrounded by increased amounts of young pale-staining connective tissue.

In adenosis, women in their late thirties or early forties predominate. As in mastodynia the women are usually childless or have not borne children recently. In this group the symptoms overlap in some degree those of mastodynia, since these patients also have painful breasts in which can be palpated dense, swollen tissue. There are, however, distinctive features. The breasts are small, dense, and transilluminate poorly. When they are lifted up and grasped between the examining fingers, a definite saucer or liver-like edge is felt. The mammary tissue contains numerous, small, discrete nodules, varying from the size of a pea to that of a marble. Microscopically, the nodular tissue is composed of small cysts or minute intracystic papillomas. The lobule formation in the affected tissue is distorted. Sprouts of unencapsulated epithelium proliferate directly into the surrounding fibrous tissue.

In cystic disease the patients affected are usually in their forties and are approaching or passing through the menopause. The breasts of these patients are of fair size, inclined to adiposity, transilluminate well and have given no previous trouble. A definite lump usually several centimeters in diameter is found. The cysts apparently make a their appearance abruptly accompanied by a slight sticking or stinging sensation. On palpation the cyst is freely movable, circular in outline, smooth and tense. Aspiration yields a cloudy fluid. If the cyst is explored it is found to have a tense thin blue wall. Microscopically the wall is composed of fibrous tissue with or without an epithelial lining. The surrounding mammary tissue shows increased amounts of fibrous tissue and involution of the lobular elements.

The clinical history in cases of mammary dysplasia suggests that the condition is dependent upon ovarian dysfunstion. In mastodynia the menstrual periods are often closer together than normal, the cycles being 25 or 26 days or less. This is particularly apt to be the case during the cycle which precedes an attack of pain and swelling in the affected breast. There is also a relatively high percentage of sterility in married women with this condition. In adenosis the menstrual periods are usually irregular. Many of these patients are approaching the menopause and have the characteristic symptoms of nervous instability. Thyroid disturbances and functional uterine bleeding may accompany this condition. In cystic disease the men-

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strual cycles have usually been normal during the preceding years but the patient at the time is approaching or passing through the menopause.

While most observers agree on the fact that mammary dysplasia is an expression of ovarian dysfunction in cyclic women, there is less agreement on the exact nature of the endocrine disturbance. Taylor in his study of the endocrinology of chronic cystic mastitis found a high incidence of menstrual disorders and cystic ovaries and concluded that the condition was associated with ovarian dysfunction in some cases. However, hormonal assays on the urine led him to conclude that a simple excess or lack of estrogenic or gonadotropic hormone was not the underlying cause. Friedman came to similar conclusions (2). It must be pointed out in this connection that endocrine assays on isolated collections of urine are unsatisfactory and total collections of the urine daily through one or more cycles are necessary adequately to study these cases. Moreover, the endocrine picture is incomplete without including determinations of corpus luteum secretion, which can be studied by measuring pregnandiol excretion.

TABLE 1

Patient	Age	Cycle	Pregnandiol	Estrogen	Remarks
Pregnandiol and Estrogen Determinations in Normal Individuals					
		days	*mg.*	R.U.	
Gos.	33	28	49.6	500	Normal (entire cycle)
Tut.	24	25	58.5	—	Normal
Wil.	23	28	25.6	826	Infected nipple
See.	25	27	40.0	—	Normal
Hun.	30	39	37.0	624	Arrested mastodynia—2 mo.
Sim.	34	25	36.7	—	Arrested adenosis—5 mo.
Wei.	33	26	26.2	302	Arrested cystic disease—21 mo.
Pregnandiol and Estrogen Determinations in Mastodynia					
Lev.	28	24	13.2	—	Bilateral
Mah.	27	25	10.5	—	Unilateral
Fir.	28	23	14.6	—	Unilateral
Cut.	34	23	6.7	—	Bilateral
Had.	33	27	9.1	447	Bilateral
McC.	33	27	14.5	368	Unilateral
Sch.	28	23	10.6	—	Bilateral
Pregnandiol and Estrogen Determinations in Adenosis					
Shep.	42	40	12.8	400	Bilateral
How.	38	25	12.6	260	Bilateral
Ang.	37	36	10.8	—	Bilateral
Flu.	27	28	10.9	1752	Bilateral—previous period 31 days
Pet.	46	22	12.4	—	Bilateral
Pregnandiol and Estrogen Determinations in Cystic Disease					
Zim.	42	23	3.3	80	Bilateral—after cyst developed
Lut.	41	27	4.9	305	Unilateral—after cyst developed
Prin.	43	26	55.6	2085	Unilateral—1 mo. before cyst developed
Gos.	34	28	22.8	—	Unilateral—1 mo. before cyst developed

The excretions of estrogens and pregnandiol in the urine during the cycle of normal women have been reported by various investigators. A large number of determinations based upon methods of extraction for total estrogens show that the normal excretion of estrogens in the urine varies between 10 and 60 R.U. per 24 hours of output. The average output in the urine for a normal cycle is variously stated as between 400 and 600 R.U. (4,000 to 6,000 I.U.) (2–5).

The corpus luteum hormone function during the menstrual cycle has been measured by determining the quantity of pregnandiol (an excretion product of progesterone) in the urine. Following ovulation, values up to 15 mg. per 24 hours are obtained. The values for the total menstrual cycle have been variously reported between 15 and 60 mg. per cycle (6–8).

In the present paper endocrine studies on a group of cases of chronic cystic mastitis are reported. The group includes 7 cases with mastodynia, 5 cases with adenosis and 4 cases with cystic disease. Four normal controls are included to which have been added three cases of arrested mammary dysplasia, one each of mastodynia, adenosis and cystic disease.

The urine of the 23 patients was assayed for pregnandiol excretion and for 12 of these patients estrogen excretion was also determined[1] (table 1). The urine collection was begun on the 11th day of the cycle and all urine excreted was collected until the onset of the next menstrual period, being assayed in 48-hour lots. Since pregnandiol excretion does not begin until ovulation the period of collection was sufficient to measure total excretion. This is not true for estrogen excretion. A loss occurred during the first 10 days of the cycle which was not measured, since the controls and test cases were both assayed in similar fashion.

Among the 23 patients there were 4 normal controls. To this control group must be added 3 cases: one, an arrested case of mastodynia treated with progesterone 6 months previously and well for 2 months; one, an arrested case of adenosis treated with estrogen one year previously and free of symptoms for 5 months and one, an arrested case of cystic disease which had a spontaneous regression following the birth of a child 21 months previously.

[1] The estrogen and pregnandiol determinations were both made on the same 48-hour specimen of urine. The total specimen was acidified to pH_6, incubated and then extracted with butanol. The separation of estrogen and pregnandiol from the butanol extract is discussed in a preceding paper (11). The pregnandiol was determined by gravimetric analysis. The estrogen determinations were made by acidifying a sodium hydroxide filtrate after precipitating the pregnandiol. This acidified solution of estrogen was extracted with ether, taken up in oil, and assayed on castrate female rats.

Among these 7 patients in the normal group the pregnandiol values ranged from 25.6 to 58.5 mg. per cycle and averaged 39.1 mg. (table 1). In the normal group there were 4 patients with estrogen determinations, ranging from 302 to 826 R.U. per cycle. These (with one exception, *Gos.*) are the determined values without allowing for a 5 to 10% loss during the first 10 days of the cycle which was not determined (fig. 1).

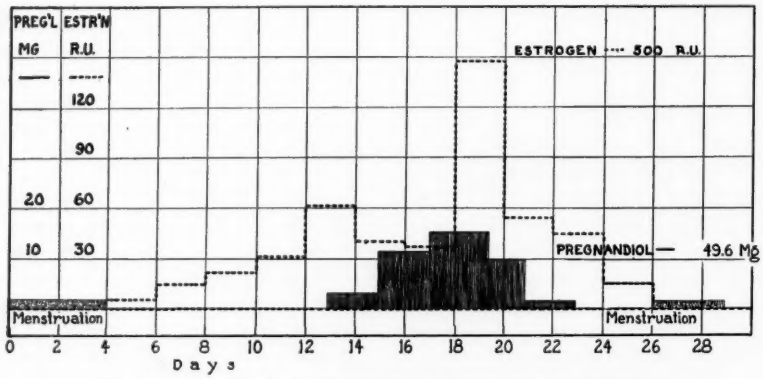


Fig. 1. Subject *Gos.* Urinary excretion of pregnandiol and estrogen in a normal cyclic woman.

There were 7 cases of active mastodynia. The pregnandiol determinations on all were low ranging from 6.7 mg. to 14.6 mg. per cycle. The average value in the 7 cases was 11.3 mg. Two of these patients had estrogen determinations (fig. 2, 3). These were within normal limits (447 R.U. and 368 R.U.). The arrested case of mastodynia showed normal values for both pregnandiol and estrogen (table 1).

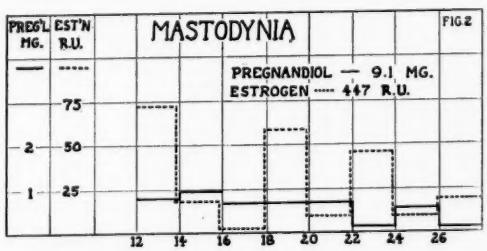
The histories of the 7 cases of mastodynia are given below.

Lev. The patient was a married women aged 28 who had had no pregnancies during 6 years of married life, although no precautions had been taken. Her cycles were 24 to 27 days. Four months previously both breasts had become painful and nodular. Estrogen therapy was given in December, 1937 with moderate improvement. In June, 1938 her symptoms recurred. The urine was assayed in June, 1938 and showed 13.2 mg. of pregnandiol per cycle; estrogen determinations were not made. The patient received progesterone therapy in August, 1938 with marked improvement. She returned in June, 1940 with mild recurrent symptoms.

Mah. The patient was aged 27 and had one child 4 years of age. Her menstrual cycles were 25 to 26 days apart. She was seen in August, 1928 for a painful tender region in the upper portion of the left breast, which was dense and swollen on palpation. Assays of urine the following month showed 10.5 mg. of pregnandiol per cycle; estrogen determinations were not made. The patient was referred to the psychiatric clinic for cancerphobia.

Fir. A women aged 28 had 3 children, the youngest 3 years of age. Her menstrual cycles were 25 to 26 days apart. She was examined in September, 1938 for a tender swollen region in the left breast. Assays of the urine in the following month showed 14.6 mg. of pregnandiol per cycle; estrogen determinations were not made. The patient reported herself improved without specific therapy one year later.

Cut. The patient was 34, had 2 children 10 and 12 years old, and previously had had 2 miscarriages. In the past 6 months her menstrual periods have lasted a week. She was seen for pain and heaviness in the left breast in February, 1938. Dense swollen tissue was palpated in the outer upper quadrant of the left breast and the right



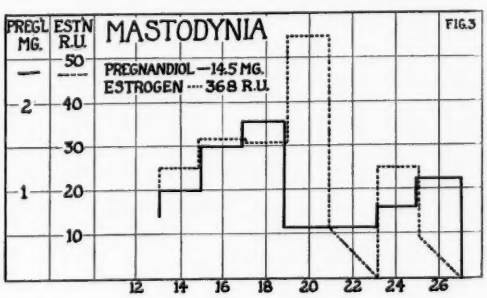


Fig. 2, 3. Urinary excretion of pregnandiol and estrogen in two cases of mastodynia. Patients *Had.* and McC. (Vertical scales on these two charts differ.)

breast was indefinitely lumpy. Assay of the urine showed 6.7 mg. of pregnandiol per cycle; estrogen determinations were not made. The patient has had a series of endocrine treatments, estrogen and later progesterone. She was well during the summer of 1938, had a small cyst in November, 1938 which diasppeared, and remained well following progesterone therapy until January, 1940. She is again being treated with progesterone.

Had. The patient was aged 33 and had 2 children, the youngest 6 years old. She had regular cycles 28 days apart. She was examined for pain and tenderness in both breasts of several months duration. A mass of tender indurated tissue was found in the outer quadrant of the right breast, the opposite breast was indefinitely lumpy. Assays of the urine in August, 1938 showed 9.1 mg. of pregnandiol per cycle and 447 R.U. of estrogen. There was a spontaneous regression of symptoms and treatment was not instituted.

McC. The patient, aged 33, was married and childless; her menstrual periods have been at 25 to 26 day intervals. Both breasts have been painful for the past 4 years. She was examined in October, 1936 for a dense swollen tender area in the upper portion of the left breast. She was treated successfully with estrogen therapy in November and December, 1936. There was a return of symptoms early in 1938. In July, 1938 assays of the urine showed 14.5 mg. of pregnandiol and 368 R.U. of estrogen per cycle. She was treated with progesterone therapy in 1939 and is well in 1940.

Sch. The patient, aged 28, was a widow without children. Her menstrual cycles varied from 23 to 26 days. She had had painful breasts for the past 3 years. She was examined in August, 1934 at which time there was tender, granular dense tissue in the upper and outer portions of both breasts. The patient was treated successfully between September, 1934 and January, 1935 with estrogen therapy. She remained well until April, 1939 when her symptoms recurred. Assays of the urine for pregnandiol were made in April, 1939 and showed 10.6 mg. per cycle; estrogen determinations were not made. The patient kept an accurate account of her symptoms during the determinations. They were as follows: March 29th to April 1st, menstruating, breasts not painful. April 3rd, breasts becoming sore but are soft and small. April 10th, quite sore generally, particularly around the edges and slightly larger. April 12th, swollen and full, sore on the outer edges. April 13th and 14th heavy, full, larger and sore everywhere to the touch. April 17th, about the same, more swollen on sides and pain radiates toward both arms. April 18th, support of brassiere needed day and night, breasts diffusely sore and about one-fourth larger. April 20th, sore, heavy, but somewhat softer. April 21st, less sore, menstruation beginning. April 25th, menses stopped. April 26th, hardly sore at all. This was a 23-day cycle.

Five cases of adenosis were assayed. The range of values for pregnandiol was similar to that found in mastodynia varying from 10.8 to 12.8 mg. per cycle. The average pregnandiol value was 11.9. Three of the patients had estrogen determinations, which varied from low, to normal, to high values, 260, 400 and 1,752 R.U. respectively. The histories of these 5 cases are given below (fig. 4, 5).

Shep. A woman aged 42 had 3 children, the youngest 11 years of age. Her menstrual periods had been very irregular for the past 4 years. Six months ago she noticed soreness and swelling in both breasts. The patient was examined in September, 1935. She was nervous and underweight. Both breasts were small, contained numerous nodules, 1 to 5 mm. in diameter, and there was a saucer-like edge along the outer borders. The patient improved on estrogen therapy followed by injections of prolactin. She remained well throughout 1936 but returned in July, 1937 with a tender dense nodular area in the right breast. This was again treated with estrogen therapy. The patient remained well until August, 1938 when she returned with tender nodules in both breasts. Assays on the urine performed in August, 1938 showed 12.8 mg. of pregnandiol and 400 R.U. of estrogen per cycle. The patient was then treated with progesterone therapy and has remained well through May, 1940.

How. The patient was single, aged 38, and had menstrual irregularities for a period of 8 years. In the past 3 years the breasts have become increasingly painful and lumpy. When examined in May, 1938 there was dense nodular tissue in the outer upper quadrants of both breasts. The breast had a definite edge. Assays of the urine in May showed 12.6 mg. of pregnandiol, and 260 R.U. of estrogen per cycle. There was a gradual improvement in symptoms during the next 2 years although specific therapy was not given.

Ang. A single woman, aged 37, had irregular menstrual periods for the past 6 years. Her breasts had been painful and lumpy for the past 4 years. When examined in June, 1938 she was nervous and underweight, and the thyroid was moderately enlarged. Both breasts were small, had a definite edge and contained numerous nodules, ½ to 1 cm. in diameter. Assays of the urine performed in June, 1938 showed 10.8 mg. of pregnandiol per cycle; estrogen determinations were not made. The patient improved on estrogen therapy but had recurrent symptoms in May, 1940.

Flu. The patient was aged 27, married but childless. Her menstrual periods had been fairly regular with 28-day cycles. She had painful, lumpy breasts for the past 2 years. In December, 1936 two nodules were excised from the left breast. The condition progressed. When examined in August, 1938 the breasts were small and had a definite edge. There was a dense elevated, tender mass of tissue about the old scar and numerous small shot-like nodules in both breasts. Assays of the urine in August, 1938 showed 10.9 mg. of pregnandiol and 1,752 R.U. of estrogen, per cycle. Progesterone therapy was advised but not given. The patient, however, reported herself improved one year later in August, 1939.

Jet. A married woman aged 46 with 3 children, the youngest 17 years old, had had irregular menstrual periods for the last 6 months. She had noted pain and nodularity in both breasts during this time. When seen in January, 1939 she was nervous and underweight. Both breasts were small, had saucer-like edges and contained multiple shot-

like nodules. There was dense swollen tissue in the midzone of the left breast. Assays of the urine showed 12.4 mg. of pregnandiol per cycle; estrogen determinations were not made. In the next 2 months a hard small nodule about 5 mm. in diameter appeared along the inner upper margin of the left breast. A biopsy was made, the lesion found to be cancerous, and a radical mastectomy was performed.

The endocrine disturbances in mastodynia and in adenosis are similar. Adenosis may be looked upon as a more advanced stage of mastodynia. This is borne out by the clinical histories. Nearly all patients with adenosis give a history of painful breasts. While the majority of cases with mastodynia, when followed for a period of 5 to 10 years, show spontaneous regression, a small group develop adenosis during such a period of time. In a series of 241 cases of mastodynia, followed for more than 5 years, 10 cases or 5% developed adenosis (9).

From an endocrine standpoint, both mastodynia and adenosis show corpus luteum deficiency. Estrogen values may be normal. From another point of view, cases with mastodynia and adenosis may be looked upon as having a relative hyperestrogen secretion. Experimentally this viewpoint is justified, since in castrated rats estrogenic stimulation alone with pellet implantations or daily injections of 5 to 10 γ of estrone for several months produces the characteristic picture of mastodynia and adenosis (10).

An inadequate number of cases of cystic disease has been studied. Two cases of cystic disease were assayed after the cysts had developed. The pregnandiol values were extremely low, 3.3 and 4.9 mg. The estrogen values were 35 and 305 R.U. (see fig. 7, 8). One case of cystic disease was assayed the month before the cyst developed. This patient was studied because two sisters had cystic disease. There was a normal pregnandiol determination (55.6 mg.) and ab-

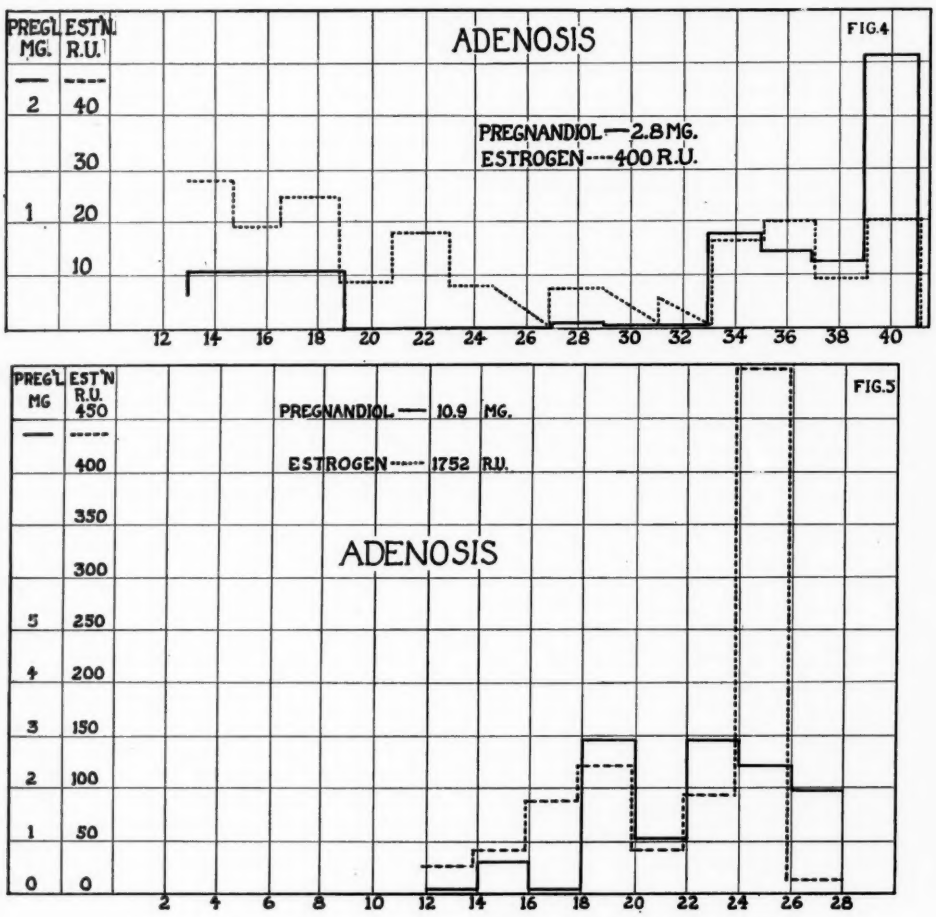


Fig. 4, 5. URINARY EXCRETION OF PREGNANDIOL AND ESTROGEN IN TWO CASES OF ADENOSIS.
Patients *Shep.* and *Flu.*

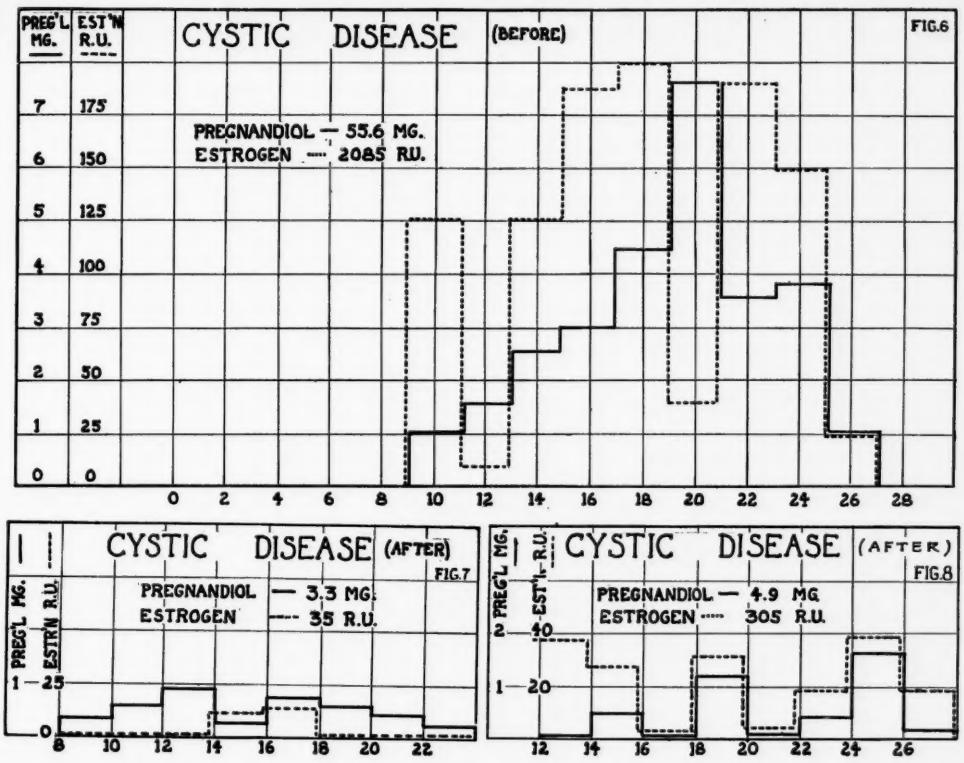


Fig. 6–8. URINARY EXCRETION OF PREGNANDIOL AND ESTROGEN IN 3 CASES OF CYSTIC DISEASE. Fig. 6. Patient *Prin.*, 1 month before cyst developed. Fig. 7. Patient *Zin.*, after cyst developed. Fig. 8. Patient *Lut.*, after cyst developed.

normally high estrogen values (2,085 R.U.) (fig. 6). The following month the patient developed a cyst. In another patient there had been normal pregnandiol values (49.2 mg.) and normal estrogen values (500 R.U.), when the patient had been studied as a control, a year previously. The patient was then studied a second time for pregnandiol, the determination showing 22.8 mg. per cycle. Unfortunately estrogen determinations were not made at this time. The following month the patient developed a cyst which was excised. The histories of these cases are given below.

Zin. A woman aged 42 with one child aged 15 had had a 24 to 25-day menstrual cycle for the past few years. She complained of pain and lumps in both breasts. Examination in November, 1938 showed adipose breasts with dense nodular areas in the outer upper quadrants. In this dense tissue there were two cysts about 3 cm. in diameter in the left breast and a smaller cyst in the right breast. In December, 1938 assays of the urine showed 3.3 mg. of pregnandiol and 80 R.U. of estrogen per cycle. In January, 1939 progesterone treatment was given (5 mg. twice weekly, a total of 40 mg.). There was some regression in the cysts, but the patient returned with active recurrence in September, 1939 when cysts in both breasts were aspirated.

Lut. A woman aged 41 with 2 children, the youngest aged 15, had had a regular 27-day cycle. Five weeks ago a lump appeared in her right breast. A tense movable nodule, 3 cm. in diameter was palpated. This was excised in August, 1938 and proved to be a cyst. Assays performed on the urine in August, 1938 showed 4.9 mg. of pregnandiol and 305 R.U. of estrogen per cycle.

Prin. The patient was aged 43 and had 4 children, the youngest aged 9. She had had regular 28-day cycles. Her breasts were examined because they were slightly tender and because both sisters were under observation for cystic disease. The breasts were adipose and pendulous and except for some thickening and tenderness in the outer upper quadrant of the right breast, the result of the examination was negative. The urine was assayed for pregnandiol and estrogen in November, 1938 and showed 55.6 mg. of pregnandiol and 2,085 R.U. of estrogen per cycle. A hysterectomy was performed for myoma of the uterus and the following month a cyst 2½ cm. in diameter developed in dense tissue in the right breast. This was successfully treated by aspiration and there has been no recurrence.

Gos. A woman aged 32 had two children, 7 and 5 years of age. She had had regular 28-day cycles. She was selected as a normal control in May, 1937 and her urine assays at that time showed 49.6 mg. of pregnandiol and 500 R.U. of estrogen per cycle. In June, 1939 pregnandiol studies were again made. A total of 22.8 mg. per cycle was obtained. Unfortunately estrogen determinations were not per-

formed at the second study. The following month the patient developed a cyst in the right breast which was treated by excision.

It is not possible to state with assurance the endocrine disturbance in cystic disease. The opinion based upon the few assays performed and the experimental production of cystic disease in animals is that the cysts develop following prolonged or intense, unopposed estrogen stimulation or after the withdrawal of a previous estrogenic stimulation.

SUMMARY

Endocrine studies on cases of chronic cystic mastitis including 7 cases of mastodynia, 5 cases of adenosis or Schimmelbusch disease, and 4 cases of cystic disease along with 7 controls are reported. Pregnandiol determinations on the urine were carried out on all of the 23 patients and estrogen assays on 12. The endocrine disturbance in the 7 cases of mastodynia and in 5 cases of adenosis were found to be similar, adenosis apparently being a more advanced stage of mastodynia. The pregnandiol values in both of these groups were low averaging 11.6 mg. per cycle as compared to 39.1 for the controls. Estrogen values may be normal. On the basis of the limited number of cases studied mastodynia and adenosis may be looked upon either as having a corpus luteum deficiency or as having a relative hyperestrinism. In two cases studied after cysts had developed pregnandiol values were low. In the cycle preceding the development of a cyst, pregnandiol output was normal and estrogen output high (2,085 R.U.) in one case, and pregnandiol values normal in the second case.

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PROGESTIN

ASSAY OF THE BLOOD OF PREGNANT WOMEN FOR PROGESTIN[1]

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THE ELABORATION of the intrauterine technic for assaying progesterone,[2] by McGinty, Anderson and McCullough (1) has opened a wide field for those concerned with assaying for the hormone of the corpus luteum. The sensitivity of this method in detecting the presence of progesterone has been found to approach a minimum of 0.06γ of the hormone. It was, however, indicated by the data of McGinty, Anderson and McCullough, and of Haskins (2) that although the intrauterine method of assay is very delicate as a qualitative test, it has little practical value as a quantitative assay method.

Since progestin had not been demonstrated in the human blood stream, it was proposed to apply the McGinty test for progesterone to extracts of the blood of pregnant women. A progesterone-like substance has been demonstrated in the blood of the non-pregnant rhesus monkey by de Allende (3), and a similar substance demonstrated in pregnant guinea pig blood by Haskins (2). That progestin had not been previously found in human pregnancy blood serum was because of the necessity of extracting 5 to 10 liters of blood to obtain enough active material to be assayed with the less sensitive technics of Corner and Allen (4) or Clauberg (5). With the possible exception of the bitterling test (6) for progesterone, only the intrauterine application method could presumably be used to demonstrate the presence of progestin in small amounts of pregnancy serum.

Twenty-one samples of blood from women in various months of pregnancy were obtained. The serum from each sample was expressed by centrifuging. In no case did the volume of serum exceed 5 cc.

Each sample of serum was shaken in a separatory funnel with 10 times its volume of ether and the ether-insoluble portion was discarded. The ethereal solution was then washed with 10 cc. of 2 N NaOH to free the extract of estrogens by precipitation as the sodium salt. The volume of the ethereal solution was reduced to 1 cc. by boiling with hot water under reduced pressure. To this residue was added a small volume of peanut oil and the remaining ether was removed by a current of air. In this manner proportionate parts of the serum extracts were dissolved in 0.1 cc. volumes of peanut oil, in which form the extracts were assayed (table 1). In several cases 0.2 cc. of untreated serum was tested.

The method of assaying the peanut oil solution was essentially the same as the technic described by McGinty, Anderson and McCullough (1). In brief this consists of priming immature female rabbits with 25 I.U. of estrogen daily, for 6 days. On the seventh day the abdomen of the animal is opened and a segment 2 to 3 cm. in length is isolated in each uterine horn by double ligatures. The solution to be tested (0.1 cc.) is injected into the lumen of one of the isolated segments, to the other segment is applied 0.1 cc. of peanut oil as a control. The animal is killed 72 hours following this operation. The uterus is removed and is examined histologically. The degree of reaction is described by the progestational proliferation of the uterus which is graded on the basis of the Corner-Allen scale. Since it had been shown (2) that only with large doses of crystalline progesterone does the activity of the injected solution spread from the isolated segment to other parts of the uterus, the technic was modified to the extent that four 2 cm. segments were isolated in each uterus so that the animals used might remain at a minimum.

A small group of animals was also used in which 3 or 4 uterine segments were isolated and to which known amounts of progesterone were applied. Comparison of the reactions obtained by the serum extract series with the crystalline progesterone series provides a rough estimate of the amount of progestin present in the serum extracts.

Control segments were made in several animals in the crystalline progesterone series and in the serum extract series. These segments were injected with 0.1 cc. of peanut oil only. Control segments were also made in animals in which no segment received a progestationally active solution.

RESULTS AND DISCUSSION

The reactions caused by injecting the several dilutions of the ethereal extract of each serum sample are indicated in table 1. With only one exception, each of the extracts in at least one of its dilutions, produced progestational proliferation. Comparison of these reactions with those obtained with the several doses of

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[2] The progesterone in this experiment was generously supplied through the courtesy of Dr. Erwin Schwenk of the Schering Corporation.

TABLE 1[1]

Animal weight	Serum 0.2 cc.	Extract of 0.4 cc. serum in 0.1 cc. oil	Extract of 0.6 cc. serum in 0.1 cc. oil	Extract of 0.8 cc. serum in 0.1 cc. oil	Extract of 1.0 cc. serum in 0.1 cc. oil	Control 0.1 cc. oil	Month of pregnancy of serum
gm.							
1019	o	+	+	+	—	—	2
1019	o	o	o	o	—	—	3
680	—	—	o–+	o–+	+	o	3
906	o	o–+	+	o–+	—	—	4
900	+	o–+	o–+	+	—	—	4
1010	o	—	o–+	+	—	—	4
906	—	o–+	o–+	+	+	—	4
1132	o	+	+	o–+	—	—	5
1100	o	—	o–+	o–+	—	—	5
1132	o	o–+	o	o	—	—	5
959	o	+	o	+–++	—	—	5
567	—	—	—	—	o–+	—	5
567	—	—	o	o	o–+	o	6
680	o–+	o	o–+	+–++	—	—	7
1130	o	o–+	+	+	—	—	7
950	o	o–+	o–+	o–+	—	—	7
680	o	o–+	o	o	—	—	7
906	o	+	—	o	—	—	7
900	—	o–+	o	o	o–+	—	7
736	—	—	+	o	o	o–+	7

[1] Reactions expressed according to Corner-Allen scale.

crystalline progesterone, table 2, indicates that the majority of the extract dilutions produced a reaction less than or equal to, that caused by 0.13γ of progesterone.

It is of interest to note that one of the control segments in the serum series, and all in the crystalline progesterone series exhibited progestational activity. That this effect is not solely due to the peanut oil is shown by the fact that controls which did not receive a solution containing progesterone but did receive 0.1 cc. of peanut oil exhibited no recognizable progestational proliferation. The effect is dependent on the peanut oil to some extent, because segments not injected with peanut oil but adjacent to a progesterone injected segment do not show a positive progestational change. This is possibly due to the solvent action of the oil which might have the effect of concentrating any progesterone obtained from the blood stream. An analogous situation has been found to exist between estrogens and peanut oil, as reported by 'Espinasse (7).

Since it is possible to demonstrate the presence of progestin in small quantities of pregnancy serum, it seems advisable to attempt to modify the intrauterine assay technic so that it may be used on a quantitative basis. If this proves possible an assay of the amounts of progestin in the various stages of pregnancy might prove to be a useful step toward the elucidation of some of the problems of the hormone of the corpus luteum.

SUMMARY

The intrauterine method of assay for progesterone as elaborated by McGinty, Anderson and McCullough, was utilized for testing the blood of pregnant women. Etheral extracts of 0.4 to 1.0 cc. of pregnancy

TABLE 2[1]

Animal weight	0.13γ progesterone in 0.1 cc. oil	0.25γ progesterone in 0.1 cc. oil	0.50γ progesterone in 0.1 cc. oil	1.0γ progesterone in 0.1 cc. oil	Control 0.1 cc. oil
gm.					
736	—	++	++–+++	+++	++
567	—	++–+++	++	++	++
906	—	+–++	++	++	+
848	+, +	+	—	—	+
567	++, ++–+++	—	++–+++	—	—
906	—	—	—	—	o, o
567	—	—	—	—	o, o
900	—	—	—	—	o, o

[1] Reactions expressed according to Corner-Allen scale.

serum produced positive progestational action, as judged on the basis of the Corner-Allen scale. Twenty samples of serum of the 21 samples tested proved positive for progestin in at least one of the dilutions of the extracts. The reactions were all minimal and indicate that the extracts of 1 cc. of serum or less probably contain less than 0.13γ of progestationally active substance.

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ADRENAL INSUFFICIENCY

SOME PITFALLS IN THE TREATMENT OF ADDISON'S DISEASE

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DURING THE PAST DECADE, the prognosis of Addison's disease has been completely altered by a series of rapidly developing events; the introduction of potent extracts in 1930; the beneficial effects of high salt feeding in 1934; the importance of an excess ingestion of sodium as compared with chlorine ions in the same year; the necessity for restriction of potassium intake in 1935; and the synthesis and isolation of crystalline hormonal material in 1936. Such changes in therapy have been briefly summarized by several observers (1–6).

In the therapeutic application of these fundamental discoveries, problems have arisen, and dangers inherent in the treatment itself are being recognized.

Adequacy of treatment is not easy to determine for several reasons. We cannot readily measure the amount of effective hormone present. Sodium and chlorides may both be normal in the blood and in the urine even in the presence of adrenal cortex deficiency (7, 8, 9). The elevation of the blood potassium is inconstant (5). Blood glucose levels and glucose tolerance are not strikingly affected by the less expensive commercial preparations available.

By no means the least of the difficulties is rooted in the fact that there are a large number of extracts of the adrenal cortex and numerous synthetic preparations, each of which only partially substitutes for the action of the normal gland. The influence of corticosterone, and its related compounds with an oxygen atom at C11, is predominantly upon gluconeogenesis and muscle efficiency. The outstanding action of desoxycorticosterone is upon the distribution of electrolytes; and the early improvement in renal function follows particularly the use of the amorphous fraction. While the selection of the therapeutic agent in the individual case might logically take these factors into account, it seems advisable to limit our comments to one of these compounds, desoxycorticosterone. It is with this compound that we have had most experience and it is the substance most widely available at the present time.

Before effective hormonal preparations had been developed, several valuable adjuvant therapeutic measures, based upon current conceptions of pathologic physiology, were employed in treating the disease. It now appears to be important to question and to revise the routine use of these procedures. In so doing, the cardiac status of the patient becomes the focal point for consideration, because this organ is severely affected. The factors primarily concerned in producing the weakened heart in the patient with Addison's disease include poor alimentation, the hemoconcentration of the blood, the alteration of electrolyte potentials across cellular membranes, the deficiency of vitamin B_1, and the drastic lowering of glycogen reserves.

Our present methods of treatment tend to embarrass still further this already overburdened circulatory apparatus (1, 10–14), and all too frequently result in death (1, 10, 15). It has been the custom to treat the patient in crisis or impending crisis vigorously with high sodium, low potassium intake, and large quantities of hormone. While such a procedure affords rapid restitution to normal of the functions with which the adrenal cortex is concerned, its intensive application has been shown to damage even a previously normal circulatory apparatus (16); that such effect has apparently not been produced by the synthetic hormone alone is possibly because sufficiently large doses have not been used. The inherent danger lies in overdoing the treatment.

In treating Addison's disease, the danger of too much salt (10, 17, 18), of too much water (10, 17), of too drastic potassium restriction (1, 19, 20), and of overdosage with desoxycorticosterone (1, 10–14, 20, 21), have been emphasized, and the resulting heart failure (10–13), muscular weakness (1, 14, 16, 20), anasarca (10, 14, 21, 22), hypoproteinemia (10), and hypertension (21, 22) have been detailed by others. Avoidance of these difficulties can be accomplished by attention to the following points.

1. Cessation of electrolyte therapy when the blood sodium value and sodium excretion approach normal.

2. Replacement of potassium in usual amounts in the diet as soon as the previously altered electrocardiogram returns toward normal.

3. The addition of vitamin B to the therapeutic regime from the beginning.

Read before the Twenty-fourth annual meeting of the Association for the Study of Internal Secretions, New York City, June 10th, 1940.

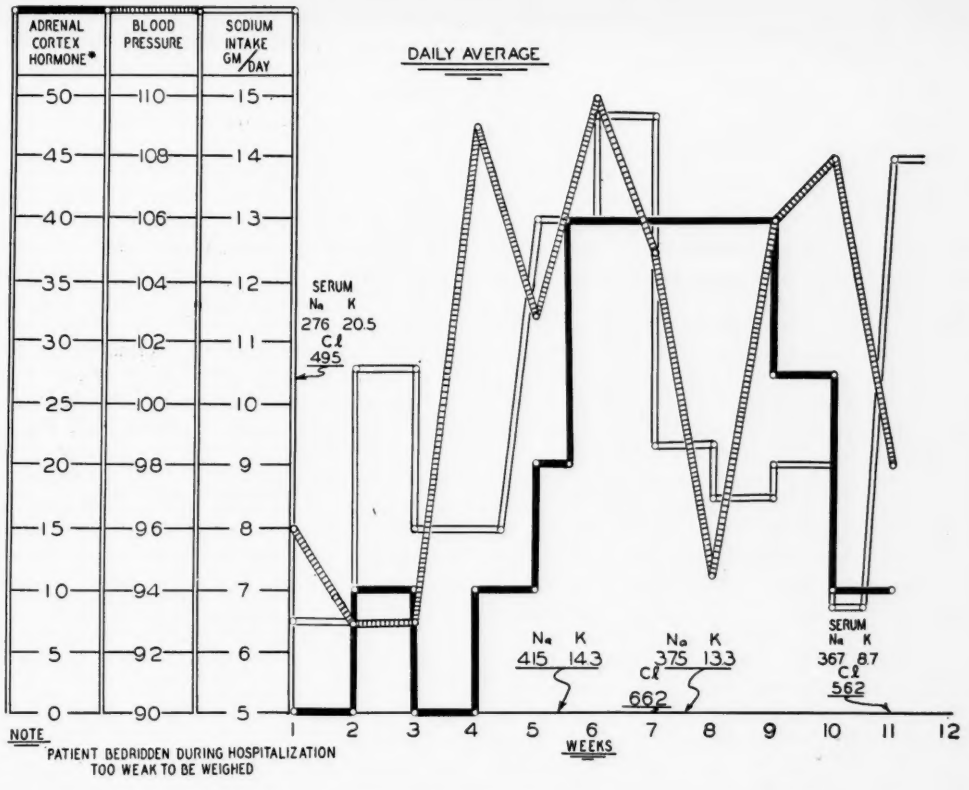
ADRENAL CORTEX HORMONE*
BLOOD PRESSURE
SODIUM INTAKE GM/DAY
DAILY AVERAGE
SERUM Na K 276 20.5 Cl 495
Na K 415 14.3
Na K 375 13.3 Cl 662
SERUM Na K 367 8.7 Cl 562
WEEKS
NOTE
PATIENT BEDRIDDEN DURING HOSPITALIZATION TOO WEAK TO BE WEIGHED

Fig. 1. Correlation of blood pressure, Na and cortical hormone intake in *case* 3 (*E. M.*).
*Adrenal cortex hormone dosage in cc. (different brands).

4. The use of cardiac mensuration as an early index of sufficient treatment.

5. Avoidance of excessive doses of hormone.

6. The application of implantation therapy only after the patient has been fully stabilized on a general mixed diet and hormone by injection.

7. Control of miscellaneous problems.

1. *Cessation of electrolyte therapy when the blood sodium value and the sodium excretion approach normal.* Emphasis upon normal blood and urinary values for sodium, chloride and potassium as indicative of control of Addison's disease was a logical outgrowth of the experiments and observations of Loeb (4, 5, 14), Wilder et al. (1, 23), Zwemer (24, 25, 26), Allers et al. (27), and others that adrenalectomized animals maintained on high sodium, low potassium regimes could be kept alive indefinitely. But a normal blood chemistry does not necessarily signify a normal person (7, 8, 9), and may lull the physician into a false sense of security or into a state of uncertainty as to diagnosis, as it did in the following instance.

E.M. (*Case III*),[1] on admission (Fig. 1), had a blood serum sodium of 276 mg.%, potassium of 20.5 mg.%, and chlorides (as sodium chloride), 495 mg.%. On moderate doses of various adrenal extracts (10 cc. daily), and a sodium intake varying from 6.5 to 10.5 gm. daily, her systolic blood pressure was raised from 90 to 108 and the electrolyte distribution of the blood restored to normal. A further increase in hormone to 20 cc. daily and a salt ingestion of 13 gm. daily produced a blood sodium level of 415 mg.%, and potassium of 14.3 mg.%. Despite these high figures, which were maintained from the 5th week after admission until the time of her death during the 11th week of her hospital stay, her course was progressively downwards. In view of the very high blood sodium, sodium ingestion was reduced to a maximum of 9 gm. daily, and during the last week of her illness to 7 gm. daily.

With this change there was at first a reduction in blood pressure and later a rise with a rapid lowering just before death. In view of the very high sodium level her large daily dose of hormone (40 cc.) was lowered with the

[1] Summaries of this and the other cases upon which the present study is based have been detailed in the following article: McGavack, Thomas H.: Changes in heart volume in Addison's disease and their significance," *Am. Heart J.*, in press. Numbering of cases is as there used.

thought in mind that perhaps low blood potassium levels might be playing a part in her asthenia. Death occurred with serum electrolytes distributed as follows (in mg.%): sodium 367; potassium 8.2; chlorides (as sodium chloride) 562.

Comment. It is not entirely clear whether death in this case was the direct result of cortical insufficiency or the presence of less than 2.5 m.eq. of potassium in the serum. Sudden rather inexplicable deaths have been noted by various observers (1, 8) in the presence of normal electrolyte distribution. Low potassium values, less than 2.5 m.eq. per liter, may be associated with paresis of skeletal muscle, and myocardial failure.

Until the advent of low potassium intake and potent adrenal cortical hormones as therapeutic measures in the treatment of Addison's disease, familial periodic paralysis was the only clinical syndrome attributed to potassium deficiency. We have therefore no clear-cut picture of potassium want as it occurs in the human being. If we may be permitted to draw analogies from the work of Kuhlman et al. (16), and of Schrader and his associates (28) with rats, it is true that the low blood potassium and lethargy present in the above patient during the last 24 hours of illness may be considered part of the picture of potassium deprivation. However, the lethargy can also be readily explained on other grounds, and the postmortem examination failed to reveal a single criterion of potassium deficiency as established by careful histologic studies (28) of animals dying as a result of low potassium intake.

Perhaps death in this case can be related to the sudden cessation of glucose infusions. Kendall (29) and Thorn (29a) have shown that the infusion of 10% glucose into adrenalectomized dogs causes at first a suppression of urine and lowering of blood potassium; but later, usually several hours after the injection, blood potassium rises, and the experiment terminates fatally with an unexplained suddenness.

In view of our experience with this patient, we have in subsequent cases always stopped the low potassium, high salt regime as soon as the blood sodium approached 330 to 340 mg.%, and the blood potassium was below 20 mg.%, with the result that we have had no further unfortunate experiences of this type. This would lead us to believe that the electrolyte disturbance was the primary underlying cause in this patient's sudden death.[2]

TABLE 1. ELECTROCARDIOGRAPHIC CHANGES AND SERUM ELECTROLYTES IN ADDISON'S DISEASE (*Case* VI)

Date	Serum		Blood N.P.N. mg.%	Electrocardiogram Lead II		
	Na	K		QRS	T	QRS:T Ratio
	mg.%			Ht. in mm.		
7/26	288	25.9	46	5.0	4.0	1.25
9/20	374	14.9		7.5	3.0	2.50
10/8	448	12.4		9.0	2.5	3.6

2. *Replacement of potassium in usual amounts in the diet as soon as possible after treatment is begun.* In those instances in which blood potassium is high it seems rational to limit the intake of that substance. Such limitation is inadvisable under hormonal therapy, particularly with desoxycorticosterone, when no evidence of potassium intoxication exists. It seems doubtful if too great a restriction in potassium intake can occur as long as no cortical hormone is supplied to the adrenalectomized animal. However, when cortical hormone and large amounts of sodium are combined with a low potassium intake, the dangers of sodium intoxication with the concomitant loss of potassium are ever present (1, 14, 16, 17, 21, 25, 30–34). Schwab and Talbott (20) and Kuhlmann (16) suggest that very low serum values for potassium may produce profound muscular and cerebral effects. In order to determine the point at which potassium restriction may be stopped, we have found it useful not only to use the blood potassium level, but also the variations in the previously altered electrocardiogram.

The electrocardiographic changes associated with Addison's disease are well illustrated in *Case* VI (table 1). On admission to the hospital in beginning crisis, the striking findings were the low voltage of the QRS complexes, the relatively high biphasic T-waves, particularly in Lead II. Under stabilization with diet and cortical hormone these findings altered toward normal. It has been customary to relate these changes directly to the blood serum potassium values. Winkler and his associates (35) have carefully studied

[2] The ability to raise or lower the blood levels of sodium and chlorides in Addison's disease by the feeding of sodium salts with or without the concomitant administration of hormone needs no emphasis. Following the observations of Loeb et al. (*J. Exper. Med.* 57: 775. 1933), the administration of large amounts of sodium, up to 18 gm. daily, was more or less routinely practiced until very recent months, and undoubtedly saved and prolonged many lives. However, it accounted also for heretofore unexplained deaths in "crisis" without the usual signs of extremely low blood pressure, loss of weight, excessive loss of sodium, increased retention of potassium, and azotemia. Cleghorn et al. (*Endocrinology* 25: 888. 1939) have had occasion to study adrenalectomized dogs maintained on high sodium, low potassium regimes. They conclude that the real danger lies in the rapid passage of water and sodium from the blood into the tissue, with the resultant edema, hemoconcentration, and increased cardiac load. Occasionally anuria may accompany, and death from heart failure ensue. Respiratory anoxemia may act in a decisive role as pulmonary edema is often present a considerable number of hours before crisis actually occurs. Irrespective of salt therapy, however, failure may be due to a severely reduced cardiac glycogen reserve (Britton et al. (*Am. J. Physiol.* 122: 446. 1938). Vitamin B_1 deficiency apparently played no part in the results of Cleghorn and associates in view of the care taken to balance the diet in all respects except for the excess of sodium and the diminution in potassium.

the electrocardiograms of dogs under the influence of gradually increasing concentrations of potassium in the serum. The severity of the changes varied directly as the serum concentration. The first changes were noted with potassium concentrations between 5.0 and 7.0 m.eq. per liter and resembled in every respect the changes described above in our *Case* VI, in which the serum value for potassium was approximately 6.5 millimols per liter. Equally significant would seem to be the ratio existing between the total amplitude of the QRS complex and that of the T-wave. This has been shown not only in animals (35), but also in cases of Addison's disease (36, 37), but has little significance except in Lead II. In the case cited, this ratio changed from a low of 1.25 on admission to the hospital, to 3.6 as the patient's adrenal condition became fully compensated (table 1).

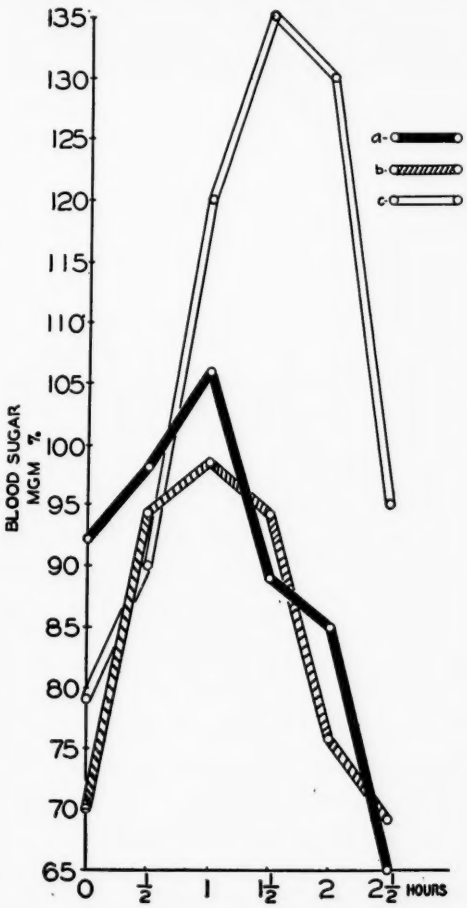

Fig. 2. Influence of desoxycorticosterone and vitamin B_1 on standard glucose tolerance curves (*case 1*). Curve a—Cortical insufficiency on low potassium diet. Curve b—Adequately treated with desoxycorticosterone and general diet. Curve c—Adequately treated with desoxycorticosterone and general diet with the addition of vitamin B_1, approximately 50 mg. weekly.

Of course, other reasons for abnormalities in the electrocardiogram of the patient with Addison's disease must not be dismissed too lightly. For instance, the fallow myocardium of any poor nutritional state may evidence QRS complexes of low amplitude. Vitamin B_1 deficiency must be thought of. Inasmuch as storage of this substance is very poor in the human body, it seems not unlikely that deficiency may rapidly develop in association with the anorexia, nausea, vomiting and weakness of crisis or impending crisis of Addison's disease. Alterations in the T-waves, extra-systoles, prolongation of the Q-T interval and other changes have been described, but Wenkebach (38), in a critical analysis of vitamin B_1 deficiency was impressed by the absence of significant change in the electrocardiogram. Moreover, were vitamin B_1 deprivation a striking factor in Addison's disease, one would expect to find a large and not a small heart. Even after blood volume has been brought to normal in the patient with Addison's disease, the heart still remains small until the patient is fully stabilized on hormonal therapy (39).

That low blood potassium is not entirely responsible for the electrocardiographic changes is shown by table 1, *Case* VI. Here a completely normal electrocardiogram was not obtained although the serum potassium had returned to well within normal limits.

Irrespective of the causes of these changes, their presence is significant, and the complete return to normal would appear to be a useful gauge in determining the adequacy of treatment.

3. *The addition of vitamin B_1 to the therapeutic regime from the beginning.* In view of certain electrocardiographic changes sometimes observed in adrenal cortical insufficiency, the presence of vitamin B_1 deficiency in Addison's disease has been suggested (40). The poor storage of this substance in man and the inadequate food intake for considerable periods of time in Addison's disease, makes such a lack seem all the more likely. That such a deficiency may be present, even during compensation of the cortical insufficiency, is supported by a study of glucose tolerance curves before and after the administration of vitamin B_1 (fig. 2). These studies were made in a 42-year-old Greek male (*Case* I) who was first seen in crisis 2 years after the onset of illness. Curve A represents the level of glucose tolerance while he was still in a state of cortical insufficiency under treatment with a high salt, low potassium diet, and cortical hormone. Curve *B* was taken 3 months later while on a general mixed diet, and adequate treatment with desoxycorticosterone. The third curve was obtained following 4 weeks of the above regime to which was added

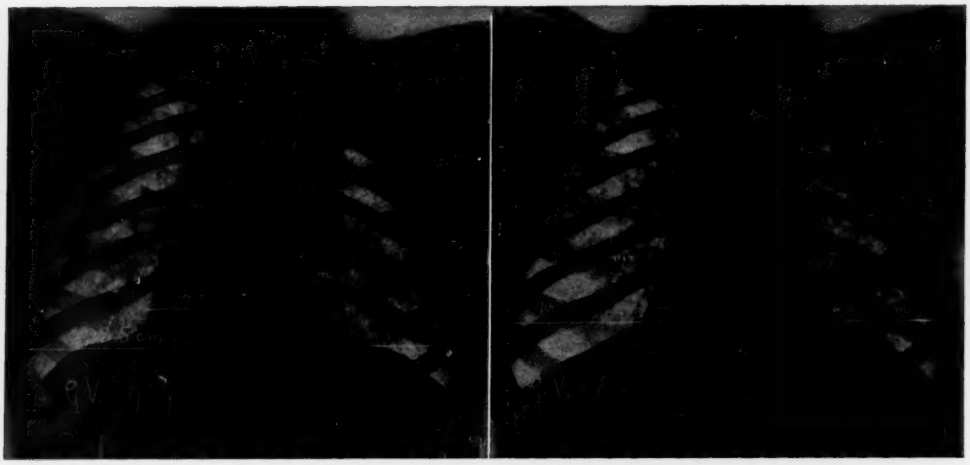

Fig. 3. (left) Two-meter x-ray of chest, before developing Addison's disease; cardiac volume per sq. meter surface 424 cc.
Fig. 4. (right) Two-meter x-ray of chest, beginning crisis; cardiac volume 302 cc. per sq. meter body surface.

the use of approximately 50 mg. of vitamin B weekly. No other change had been made in his therapy. Therefore we are inclined to believe that the increased ability to mobilize sugar can be rightfully attributed to the use of the vitamin B preparation. On other grounds, namely the diminished excretion of thiamin chloride in the urine of the patient with cortical insufficiency, Ferrebee and his associates (10) also suggest that a deficiency of vitamin B may occur in the patient with adrenal cortical insufficiency.

4. *The use of cardiac mensuration as an early index of sufficient treatment.* Details of studies of cardiac size in 6 proven cases of Addison's disease have been given elsewhere (39). The changes observed by x-ray in the individual before the onset of Addison's disease, and at the beginning of crisis are illustrated in fig. 3, 4 (*Case* II). In the course of a progressive bilateral caseous pneumonic tuberculosis this individual developed cortical insufficiency from which he died several days after the second roentgenogram. His blood pressure at that time was 78/50, serum sodium 292.3 mg.%, serum potassium, 31.7 mg.%, and a total blood volume of 3680 cc., as contrasted with a theoretical normal of approximately 4400 cc.

The simplest index of heart volume changes in Addison's disease and their significance in guiding therapy is given by the cardio-thoracic ratio. Ratios below 0.32 were only seen in crisis. Ratios below 0.40 invariably attended states of cortical insufficiency, and ratios in satisfactorily stabilized individuals ranged from 0.41 to 0.46. The use of the cardio-thoracic ratio proves fallacious only in those individuals who have flat chests, of which one instance was observed (*Case* III) (fig. 1). Even this variant can be taken into account by serial examinations beginning as soon as the patient is able to have a 2 meter chest film taken.

Inasmuch as the lateral horizontal depth diameter varies but slightly in any given patient the frontal cardiac area serves as a further check upon the cardio-thoracic ratio. Areas below 77 sq. cm. were only observed in crisis, and corresponding estimated heart volumes were less than 300 cc. When the heart volume is brought into relationship with the theoretical normal for a person of the same bodily surface area, it will be observed that the reduction is greatest in crisis (31.9%), still marked in cortical insufficiency (16.1%), and within normal range in the fully stabilized individual (fig. 5). Blood volume appears to be the major factor in the discrepancy between the size of the heart of the patient in crisis and that of the individual with varying degrees of insufficiency (39). From an analysis of these observations it seems safe to conclude that forced salt feeding and potassium restriction should be stopped when the cardio-thoracic ratio reaches 0.40, and that a diminution in the dose of cortical hormone may be advisable when this ratio rises above 0.45. Inasmuch as it is not practical to repeat roentgenographic examinations too frequently, the blood pressure may be used as a gross guide to the necessity for such studies. A roughly linear relationship appears to exist (fig. 6). It is certain that pressures within the normal range of values should justify a study of cardio-thoracic relationships.

5. *Avoidance of excessive doses of hormones.* Until very recently it was commonly felt that overdosage with adrenal cortical hormones was impossible. Now that potent extracts and effective synthetic material are available, the toxic action of adrenal cortex preparations is being recognized. In analyzing and avoid-

ing such action it must be remembered that the secretion of the adrenal cortex, like every other autocoid in the body exerts a regulatory effect upon functions which can be carried out under optimal conditions without it. Its focal point of attack nevertheless still remains in obscurity, and we may only perceive its action through variations in certain bodily processes.

6. *Variability in the absorption of crystalline hormone subcutaneously implanted.* Thorn and his associates (41, 42, 43) have estimated the average needs of the animal or human being in the following way. The subject is stabilized by the use of daily or alternate daily injections of desoxycorticosterone until the average daily maintenance requirement has been ascertained. One or more pellets is then implanted subcutaneously and further tablets are supplied if a good clinical condition is not maintained. After an arbitrary period, pellets are removed, desiccated to constant weight, and the daily average absorption calculated. The estimates of the above workers represent an average from several patients, in whom, however, the recorded individual variation appears to have been relatively small. It is their conclusion that absorption varies directly as the pellet surface and the surface area and softness of the pellet. Further, they note that the needs of the patient are about three-fifths the amount required when daily injections of the oily suspension are used. The results of their work are summarized in table 2. Wilkinson's (19) estimates are slightly higher (table 2). In studies with two patients, using tablets of identical size, obtained from a single source,[3] and compressed under standard conditions, we have found reasonably wide variations in absorption from 0.36 mg. to 0.48 mg. per 100 sq. mm. of surface, and a daily absorption per tablet of from 0.9 mg. to 1.2 mg., or a 33% variation (table 2). Equivalents in terms of the oily suspension or aqueous extracts previously used have varied in even greater degree. It would seem, therefore, that factors in addition to the physical characteristics of the inserted tablet must be taken into consideration in determining dosage.

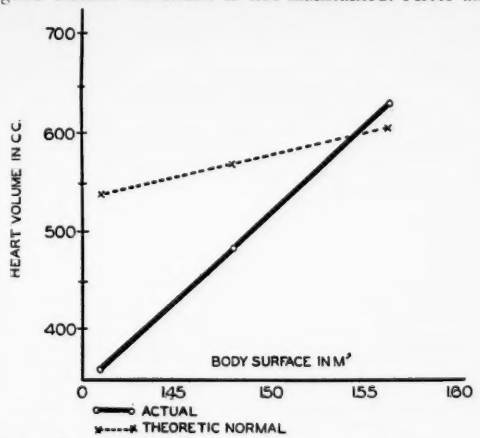

Fig. 5. Composite curve from 19 observations in 6 patients.

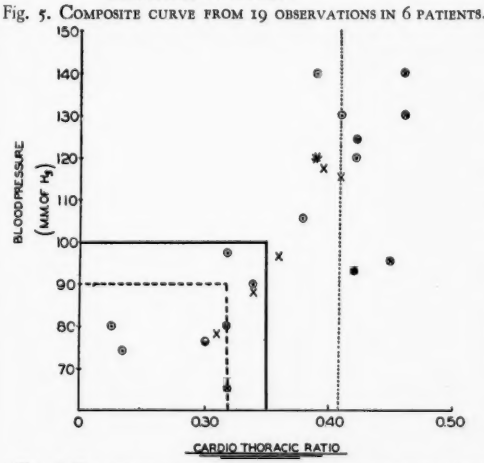

Fig. 6. Relationship of blood pressure and cardiothoracic ratio. Area enclosed by broken line represents stages in crisis; area between broken line and solid line, impending crisis; area outside solid line, insufficiency without crisis. ●This case with horizontal depth diameter of heart 7.9 cm. was in crisis.

The patient in crisis demands proportionately more hormone than the same patient later. Under good care, the diminishing need for exogenous hormone may take place steadily over a period of at least several weeks. Therefore, the calculated needs of the patient today may not be suitable for him in two to four weeks. We have heard of at least one rather disastrous result from the implantation of 1800 mg. (12 pellets) into a man, for whom the dosage was calculated on the basis of Thorn's (42) and Firor's (43) work. Generalized anasarca, pulmonary edema, heart failure, and hypertension supervened within ten days, and were fortunately relieved by routine measures and the removal of 8 of the 12 pellets. Two factors may have contributed: the source of material may have been different, and the patient may not have been fully stabilized. To avoid this pitfall, it would seem wise to control the patient on a standard general diet with or without the addition of moderate amounts of sodium (a total of 7 to 9 gm. daily, i.e., slightly above the normal intake, is satisfactory) until the amount of desoxycorticosterone necessary to maintain a good clinical condition has become stationary. This will usually take several weeks.

Other variants in determining the amount of hormone to be implanted are not so easily appraised. It seems logical to presume that local blood supply surrounding the implant may vary not only from patient

[3] We are indebted to Dr. Max Gilbert of the Schering Corporation for both the pellets and oily suspension of desoxycorticosterone used throughout these studies.

TABLE 2. VARIABILITY IN ABSORPTION OF DESOXYCORTICOSTERONE ACETATE FROM SUBCUTANEOUS IMPLANTS

Observer or Case	Wt. of tablets	Surface area	Estimated daily absorption per tablet	Actual daily absorption		Therapeutic effect of each mg. absorbed equivalent to	
				per 100 sq. mm. surface	per tablet	Oily suspension	Aqueous extracts
Thorn	*mg.* 50–150	*sq. mm.* Variable	*mg.*[1] —	*mg.* 0.25	*mg.* —	*mg.* 2.0	*cc.* —
Firor	100–125	—	—	—	0.3	2.0	—
Wilkinson	100–150	—	—	—	0.6	3.0	9–18
Case I	150	250	0.63	0.48	1.2	2.0	6– 9
Case VI	150	250	0.63	0.36	0.9	2.8	4– 6

[1] Using Thorn's original communications as a standard.

to patient but also from implant to implant in the same patient. Rates of absorption are now being estimated in our patients in an effort to ascertain the presence or absence of such variation. Ryan and McCullagh (21) claim that 400 mg. of desoxycorticosterone acetate produced no therapeutic effect whatsoever, although subcutaneous injections of oily suspension were of value. No explanation was given, but the condition of local absorption may have played a part.

It seems to have been rather conclusively shown both in animals and human beings that the patient's need for hormone does not materially alter the rate of absorption. Therefore it is necessary to estimate the number of pellets upon the basis of surface area, hardness, and previous maintenance dosage. Firor (6, 43) has implanted 12 pellets (from 1200 to 1500 mg.) in a single patient with good results. But it must be reemphasized that such a procedure is dangerous until the daily dose of hormone by injection has reached a reasonably stationary point.

7. *Other problems.* Failures in management of the patient with Addison's disease may depend upon failure to protect the patient from the abnormal stresses of life. Included in this group, treatment for which has been repeatedly emphasized, are intercurrent infections (7, 11, 15, 18, 44), operations and trauma (1, 45, 44), diseases in other glands, notably thyroid and pancreas (44–49), toxic effects of drugs (44), especially purgatives and opiates (13, 45), and over-exertion. One of our patients has developed signs of relapse bordering on crisis while under treatment, as a result of repeated febrile episodes due to upper respiratory infection. Suffice it to say that these complications should with one accord warrant the close supervision accorded the patient in crisis.

SUMMARY

The rapid advances in our knowledge of Addison's disease have created new therapeutic problems, chief of which is the cardiac condition. Several factors combine to damage the heart severely in Addison's disease.

During the treatment of Addison's disease, cardiac damage may be increased by excessive salt or water ingestion, severe curtailment of potassium intake, and overdosage with adrenal cortical hormone. Muscular weakness, anasarca, hypoproteinemia, and hypertension may accompany.

These difficulties may be avoided: (*a*) if electrolyte therapy is stopped when blood and urine sodium and potassium values approach the normal; (*b*) if vitamin B is made a standard part of the therapeutic regime; (*c*) if cardiac mensuration is utilized as an index of treatment. A cardio-thoracic ratio below 0.32 usually means crisis. Ratios above 0.41 have only been seen in fully stabilized patients; (*d*) avoidance of excessive doses of hormone, and (*e*) the application of implantation therapy with the recognition of the fact that rates of absorption may vary from individual to individual, and in the same individual, following different implantations.

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Therapeutic Symposium

TREATMENT OF ADDISON'S DISEASE

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PREVIOUS TO 1930 the usual duration of life of patients with Addison's disease was less than two years (1). Today, it is possible to extend greatly the period of survival and, in some instances, to restore patients to a life of normal, if limited, activity and economic independence (2). Three important contributions have made possible this remarkable advance in therapy: (*a*) the successful preparation of potent adrenal cortical extracts (3, 4); (*b*) an understanding of the disturbance in sodium and potassium metabolism which occurs in adrenal cortical insufficiency (5–9); and (*c*) the synthesis of a crystalline adrenal cortical hormone, desoxycorticosterone (10).

PRESENT CONCEPT OF THE DISEASE

Typical signs and symptoms of adrenal cortical insufficiency rarely become manifest until extensive destruction of functioning adrenal cortical tissue has occurred (11). Although tuberculosis remains the highest single etiological factor responsible for the disease, it is of interest to note that in a recent study no evidence of tuberculosis could be demonstrated clinically or by x-ray in a majority of 30 patients (2).

As might be anticipated, a reduction in the quantity of hormone secreted by the adrenal cortex is followed by multiple disturbances in body function. In our present state of knowledge it appears that in the human the function of the adrenal cortical hormone is concerned with the regulation of (*a*) elecrolyte and body water distribution, (*b*) carbohydrate metabolism and (*c*) pigment metabolism. Following a reduction in circulating adrenal cortical hormone there is an increased renal excretion of sodium and chloride with a striking decrease in plasma volume, which results in dehydration and hypotension (9, 12). If excessive, the sodium, chloride and water loss may result in severe dehydration with consequent impairment in renal function (pre-renal azotemia). It is probable that in addition to signs and symptoms which may be attributed to fluid loss, certain disturbances in function may be related to the altered sodium-potassium ratio which results from the retention of potassium during the period of increased sodium and chloride excretion (8).

In patients with Addison's disease, in the absence of complications, the life maintaining action of adrenal cortical hormone parallels its salt and water retaining property. However, in addition to the effect on electrolyte balance the adrenal cortical hormone has a direct effect on carbohydrate metabolism which is manifested (*a*) in the control of carbohydrate oxidation and (*b*) in the regulation of gluconeogenesis (13). Patients with Addison's disease, in whom the blood pressure, plasma volume and electrolyte balance have been restored to normal, may live comfortably without receiving the carbohydrate factor in adrenal cortical extract as long as adequate carbohydrate is ingested and absorbed (2). However, under conditions of increased carbohydrate requirement or decreased intake (starvation, fever, infection, gastro-intestinal disturbances, etc.) as the result of the oxidation of available carbohydrate and an inability to form new carbohydrate from non-glucose sources (gluconeogenesis), hypoglycemia with fatal outcome may ensue unless carbohydrate is administered parenterally or adrenal cortical extract containing the carbohydrate factor is administered in large doses.

To date, little is known concerning the disturbance in pigment metabolism which occurs in Addison's patients. Complete disappearance of abnormal pigmentation has been observed only rarely in patients treated with the available hormone preparations.

AIM OF TREATMENT

The aim and expectation of successful treatment should be the restoration of patients to a life of normal activity.

METHODS OF APPROACH IN TREATMENT

A. Measures directed towards regeneration of adrenal cortical cells
   1. Adenotropic hormone (anterior pituitary extract)
   2. Specific vitamin?

B. Gland transplants
C. Specific hormone therapy
  1. Adrenal cortical extract
    a). Oral administration
    b). Subcutaneous, intramuscular or intravenous administration
  2. Synthetic desoxycorticosterone acetate
    a). Intramuscular administration
    b). Subcutaneously implanted pellets
  3. Crystalline steroid compounds obtained from adrenal gland
D. Supplementary treatment
  1. Sodium chloride therapy
  2. Low potassium diet
  3. Adequate carbohydrate in diet

A. Regeneration of adrenal cortical cells. Those patients who show marked remissions, during which they can get along without specific therapy, probably have had regeneration of adrenal cortical tissue. However, most patients with classical Addison's syndrome fail to regenerate sufficient tissue to permit resumption of normal activity without supplementary therapy.

The demonstration that removal of the anterior pituitary gland results in striking atrophy of the adrenal cortex (14) suggested that treatment with the adrenotropic factor (15) of anterior pituitary extract might be useful in stimulating regeneration of adrenal cortical cells in patients with Addison's disease. Thus far, in the author's experience, striking benefit from this form of therapy has not been observed. It is possible that (*a*) an insufficient quantity of active hormone was used, (*b*) that a resistance to the hormone action may have been built up by repeated injections, and (*c*) that destruction of the adrenal cortex was so extensive as to offer little or no opportunity for significant regeneration. It would appear that this form of therapy should be considered seriously when adequate quantities of potent material are available.

Recently, Daft and Sebrell (16) have observed "extensive hemorrhagic necrosis of the adrenal glands of rats on deficient diets. The condition appears to be due most probably to a deficiency in some unidentified dietary factor. These animals have not shown the purpura or bone marrow changes reported by other investigators in rats on diets deficient in various factors of the vitamin B complex." No evidence whatever has been presented showing that this factor is of any clinical significance in the treatment of patients with Addison's disease.

Although experimental evidence (17) indicates that atrophy of the normal adrenal cortex may follow excessive hormone therapy in normal animals, it is not likely that this fact is of clinical significance since well marked signs and symptoms of Addison's disease rarely are observed until extensive destruction of adrenal cortical tissue has occurred. At present it would seem to be entirely unjustifiable to withhold specific substitution therapy from a patient with Addison's disease in whom sodium chloride therapy alone was ineffective in completely restoring the patient to normal activity.

B. Gland transplants. Experimentally it has been possible to maintain the lives of adrenalectomized rats by autoplastic transplants of adrenal cortical tissue (18, 19). Transplantation in species higher than the rat, *e.g.*, in the dog and in man, has not been successful, or at best has been only of temporary or questionable value. Survival and growth of human transplants would, if feasible, offer an excellent method of treatment.

C. Specific hormone therapy. Under resting or basal conditions it seems likely that the body's need for hormone is supplied by the secretion of a more or less constant quantity of hormone, conditions of stress being met by an increased secretion of hormone. Ideally this should be the aim of substitution therapy.

It is obvious that the oral administration of hormone would be the simplest method. There are two disadvantages to giving hormone by this route. *1*). The requirement of hormone administered orally appears to be at least three or four times that required by injection. *2*). There is no assurance that uniform absorption takes place when hormone is administered orally. This is a matter of serious consideration in the treatment of patients with Addison's disease who are known to be particularly susceptible to gastro-intestinal disturbances. The best results with aqueous extracts of adrenal cortex are obtained when the total daily dose of hormone is divided and injected subcutaneously or intramuscularly at frequent intervals (6–8 hours) since a single daily injection of aqueous adrenal cortical extract does not provide a uniform quantity of hormone throughout a 24-hour period.

Administration of a solution of desoxycorticosterone acetate in oil is an effective form of therapy (12, 20, 21). A single daily injection of a solution of hormone in oil gives a more prolonged effect and a more uniform rate of absorption than treatment with a single daily injection of aqueous extract. However, even the intramuscular injection of a solution of hormone in oil is less efficient than hormone absorbed slowly from hard pellets of crystalline hormone implanted subcutaneously (22).

Unfortunately, crystalline steroid compounds derived from the adrenal cortex and possessing carbohydrate-regulating property (23, 24, 25) are not available commercially. It is unlikely that these compounds will be made available for clinical investigation until a suitable method for synthetic preparation

has been perfected. It is possible that a mixture of one of these compounds, i.e., compound *E*, Kendall (13) and desoxycorticosterone acetate would provide a suitable type of therapy for correcting the disturbance in both electrolyte and carbohydrate metabolism.

At present three problems exist in regard to specific hormone therapy. *a*). Potent adrenal cortical extracts which presumably contain all essential factors are almost prohibitive in cost for most patients if adequate quantities are to be administered. *b*). Synthetic adrenal cortical hormone, desoxycorticosterone acetate, although less expensive than the aqueous extract of the adrenal cortex, is deficient in the carbohydrate regulating factor. *c*). It is difficult to adjust treatment so that at all times an adequate concentration of hormone is maintained.

D. Supplementary treatment. Supplementary sodium chloride therapy greatly reduces the requirement of hormone and hence the cost of treatment. Furthermore it is possible for some patients to resume a life of fairly normal activity when treated with added sodium chloride alone. The intolerance of patients to sodium chloride, administered orally, often limits the quantity of supplementary treatment which may be given.

A diet low in potassium has been found to be particularly beneficial for patients with Addison's disease (8). Such a diet also reduces the requirement of hormone and may, in some cases, permit patients to resume a life of reasonably normal activity without hormone therapy. It is generally agreed, however, that there is little need for a patient to continue a diet of low potassium content when specific hormone therapy is being administered; particularly is this true during the administration of desoxycorticosterone acetate.

Unless adequate quantities of the specific carbohydrate factor present in active cortical extracts but absent from desoxycorticosterone are being given to patients with Addison's disease, great care should be taken to provide frequent feedings of a diet high in readily available carbohydrate.

CLASSIFICATION OF PATIENTS

In order to facilitate a discussion of treatment, patients with Addison's disease have been classified arbitrarily into three groups, as follows.

Group A. Patients who require only added NaCl therapy, or a low potassium diet, or both.

Group B. Patients who, in addition to sodium chloride therapy, require at frequent intervals supplementary hormone treatment if relapses are to be avoided.

Group C. Patients who require continued hormone therapy.

Group A. Frequently the presence of the disease first becomes manifest during the course of an intercurrent infection or gastro-intestinal upset. Following the subsidence of the complication the patient improves sufficiently so that added sodium chloride therapy alone is adequate.

From 5 to 20 gm. of NaCl may be given daily (enteric coated 1 gm. sodium chloride tablets are a convenient means of administering salt and reducing gastric irritation). Less discomfort is noted when the salt tablets are ingested with food. A few patients prefer to take sodium chloride on cereal, in tomato juice, etc.; some prefer to drink a dilute solution of sodium salts (sodium citrate 5 gm., sodium chloride 10 gm., lemon juice 80 cc., sugar 160 gm. with a quantity of water and ice sufficient to make 1,000 cc.). In the absence of measurable renal insufficiency it is not necessary to give combinations of sodium salts, i.e., 2 parts NaCl and 1 part Na citrate, in an effort to reproduce the respective concentrations of sodium and chloride as they occur in the blood serum. It is possible that restriction of potassium intake (26) in addition to added sodium chloride therapy may enable some patients to lead a normal life without requiring hormone therapy.

Group B. In this group of patients one is likely to encounter enthusiastic opinions as to the efficacy of treatment with various hormone preparations. This is readily understood when it is appreciated that the hormone requirement of these patients is small and frequent spontaneous remissions occur. Many of these patients may be maintained in good condition for many months by administering 5 to 15 gm. of sodium chloride daily with supplementary adrenal cortical hormone therapy as indicated by the occurrence of fatigue or nausea. One of four types of hormone preparations may be used for a few days; (*a*) large doses of adrenal cortical extract by mouth (400–1,200 gm. of adrenal gland daily); (*b*) smaller quantities of aqueous extract, 1 cc. injected two or three times daily (100–150 gm. of adrenal gland daily); (*c*) a single daily intramuscular injection of 1–2 mg. of desoxycorticosterone acetate in oil.

Group C. In addition to supplementary sodium chloride therapy these patients require adrenal cortical hormone at all times. It is doubtful whether the hormone requirement of these patients can ever be satisfactorily provided for any prolonged period by the oral administration of preparations available today. Satisfactory results in most cases may be obtained with: (*a*) 2 to 3 cc. of adrenal cortical extract injected subcutaneously 2 or 3 times daily (a total of 300–450 gm. of adrenal gland daily) in addition to 5 to 15 gm. of supplementary sodium chloride therapy; or, (*b*), a single daily intramuscular injection of 2 to 5 mg. of desoxycorticosterone acetate in oil, with or without 2 to 5 gm. of added NaCl therapy; or, (*c*),

pellets of desoxycorticosterone acetate implanted subcutaneously (1 pellet of 125 mg. for each 0.5 mg. of injected hormone required for maintenance) with or without supplementary sodium chloride therapy.

It is also possible to employ a combination of two forms of specific therapy (27). Under these conditions a quantity of desoxycorticosterone acetate (either a daily injection of hormone in oil or pellets implanted subcutaneously) which will restore blood pressure and electrolyte balance, is supplemented by the addition of smaller doses of aqueous adrenal cortical extract (2–3 cc. daily, total of 100–150 gm. adrenal gland).

In rare instances complications (anemia, hypoproteinemia, phlebitis, hypertension, renal disease and cirrhosis of the liver) limit the quantity of specific hormone therapy which may be given because of the excessive sodium, chloride and water retention which accompanies adequate therapy (2).

TREATMENT OF ADRENAL CRISIS

1st Day. Upon admission to hospital the patient is placed in a warm bed and an intravenous infusion consisting of 1,000 cc. of 1.5% sodium chloride solution and 1,000 cc. of 5 to 10% glucose solution is begun immediately; 25 cc. of aqueous adrenal cortical extract are added directly to the intravenous infusion. If the systolic blood pressure is less than 70 mm. of Hg, 0.5 cc. of epinephrin is administered subcutaneously; at the same time 25 cc. of aqueous adrenal cortical extract is injected subcutaneously; and 25 mg. of desoxycorticosterone acetate in oil is injected intramuscularly in divided doses. The intravenously administered aqueous extract provides hormone for immediate use. The subcutaneously administered aqueous extract exerts its maximum effect 2 to 6 hours after administration and the intramuscularly administered synthetic hormone in oil provides a continued effect throughout the 24-hour period. No unnecessary physical examinations are permitted at this time.

Since hypoglycemia frequently complicates adrenal crisis,[1] great care is taken to maintain a normal blood sugar level throughout the first 48 hours of treatment. During the second 12-hour period an additional intravenous infusion of 500 to 1,000 cc. of normal saline solution and 500 to 1,000 cc. of 5 to 10% glucose solution is given.

2nd Day. Five cc. of adrenal cortical extract should be given every 4 to 6 hours throughout the day and night in addition to a single intramuscular injection of 10 to 15 mg. of desoxycorticosterone acetate in oil. An intravenous infusion consisting of 1,000cc. of normal saline solution and 1,000 cc. of glucose solution (5–10%) is given once throughout this period. The patient is encouraged to take frequent small feedings of milk, ginger ale and fruit juice. If liquids are not tolerated by mouth, an additional intravenous injection of saline and glucose is given during the second 12-hour period of the second day.

3rd Day. Adrenal cortical extract, 5 cc. is given twice during the third day in addition to a single injection of 10 mg. of desoxycorticosterone acetate in oil. If fluids and soft diet are not tolerated the intravenous infusions of glucose and saline are repeated.

4th Day. It should be possible by this time to give 3 to 6 gm. of sodium chloride (1 gm. enteric coated tablets) by mouth. If food and liquid are being tolerated the hormone requirement may be provided by a single injection of 10 mg. of desoxycorrticosterone acetate in oil. If sodium chloride is not tolerated by mouth, an equivalent quantity (6 gm.) is given parenterally. The appearance of edema indicates excessive sodium chloride and hormone therapy and the dosage of one of these medications should be reduced promptly.

5th Day. With a constant intake of 6 gm. daily of added sodium chloride a single daily injection of desoxycorticosterone acetate (usually 2–5 mg.) sufficient to maintain body weight is given. The patient is provided with a diet high in readily available carbohydrate. Should episodes of hypoglycemia complicate the subsequent convalescence, large quantities of adrenal cortical extract (5–10 cc., equivalent to 250–500 gm. adrenal gland) should be given every 4 to 6 hours.

INSTITUTION OF TREATMENT IN UNCOMPLICATED CASES

For patients presenting less severe symptoms of deficiency, it is desirable to test first, the response to added sodium chloride therapy alone. Thus, 2 to 3 gm. of sodium chloride (enteric coated tablets) may be given 3 or 4 times daily (a total of 6–12 gm. daily) with food. If remarkable improvement does not follow the addition of 9 to 12 gm. of sodium chloride to the regular diet it is evident that the patient requires supplementary hormone therapy. If adrenal cortical extract is used it is well to maintain an intake of 8 to 10 gm. daily of sodium chloride, injecting 2 to 3 cc. of aqueous extract subcutaneously two or three times daily (4–9 cc. daily total, equivalent to 200–450 gm. adrenal gland). The daily requirement of hormone can be determined by trial. As criteria of adequate

[1] Recent studies (13) indicate that 2–3 hours after glucose administration, patients with Addison's disease may exhibit a marked hypoglycemic reaction. For this reason great care must be taken to provide supplementary carbohydrate following glucose infusions unless large quantities (25–50 cc.) of adrenal extract (equivalent to 1,250–2,500 gm. of adrenal gland daily) are given. If fruit juice and ginger ale cannot be taken at this time parenterally administered glucose solutions must be continued. It is possible that sudden deaths which have been reported in patients with Addison's disease who have made an initial satisfactory response to intravenous therapy may be accounted for by this mechanism.

therapy one should expect restoration of weight and blood pressure as well as the concentration of serum electrolytes. If synthetic desoxycorticosterone acetate is used, it is well not to give more than 5 gm. daily of supplementary sodium chloride. Maintaining the daily intake of sodium chloride constant, 2 to 5 mg. of synthetic hormone in oil is injected intramuscularly once daily. The most striking immediate effects of synthetic hormone treatment are a rapid gain in weight associated with a retention of sodium chloride and water and a marked increase in plasma volume (hemodilution) (12). Failure to gain weight within 48 to 72 hours after hormone therapy has been instituted, is the first indication of insufficient dosage. Too rapid gain in weight (more than 0.5 kg. daily during the first week of treatment or more than 0.3 kg. daily subsequently) if continued, indicates overdosage and will result in the appearance of edema if the dose of synthetic hormone is not reduced promptly. The maximum blood pressure rise following synthetic hormone treatment may not occur until treatment has been continued for 4 to 16 weeks.

In general small quantities (1 to 3 mg.) of synthetic hormones are indicated in the treatment of patients past middle life since the great increase in blood volume, the rise in blood pressure and the increased physical activity which follow the institution of desoxycorticosterone acetate therapy place, rather suddenly, a considerable additional load on the cardiovascular system. It is well to limit the resumption of normal activity of patients in the advanced age group or of patients who have lived a life of chronic invalidism for a prolonged period immediately preceding the institution of treatment.

SUBCUTANEOUSLY IMPLANTED PELLETS OF CRYSTALLINE HORMONE

It has been observed that subcutaneously implanted pellets of crystalline hormone provide an efficacious and efficient method of administering desoxycorticosterone acetate (2). The desirability of implanting pellets of crystalline hormone may be considered after a patient has been maintained in good condition for a period of one month or more with daily injections of the hormone in oil. Pellets should be implanted only after careful clinical control has permitted the daily requirement of hormone to be determined accurately.[2] It requires at least 4 weeks and usually 8 to 10 weeks to establish with certainty the optimum daily maintenance dose of hormone in oil.

Calculation of pellet requirement. The number of pellets to be implanted is calculated directly from the quantity of hormone which is required to maintain a patient in good condition. For each 0.5 mg. of hormone so required by daily injection, one pellet of 125 mg. is implanted. The daily maintenance dose of hormone in oil is determined during a period in which the patient is receiving a constant quantity of added sodium chloride (5 gm. daily). It is desirable to use added sodium chloride therapy in preparing patients for pellet implantation, since this permits a reduction or withdrawal of the sodium chloride at any future date and thus provides a very convenient means of balancing any possible excess of hormone. Pellets weighing 125 mg. should provide effective therapy for a period of approximately 12 months. As the absorption of the pellets becomes complete, symptoms of insufficiency (loss of strength, loss of weight, lowering of blood pressure) may appear. When these signs and symptoms first appear added sodium chloride may be tried as supplementary treatment. If added sodium chloride treatment is not adequate a daily dose of hormone in oil is injected. When a new constant level of injected hormone has been reached, pellets may then be reimplanted. There are three advantages in using pellet implantations: first, the necessity for daily injections of hormone is obviated; second, a more uniform rate of absorption of hormone is obtained and third, there is a great saving in the quantity of hormone required. The only obvious disadvantages are: (*a*) the necessity of a minor operation for the implantation which is carried out under local anesthesia; and (*b*) the need for supplementary injections of hormone during periods of stress (i.e., infections, gastro-intestinal disturbances, etc.).

If the original assay has been carried out carefully over a period of 4 to 6 weeks it is rarely necessary subsequently to remove pellets because of overdosage. In the event that signs and symptoms of overdosage do become manifest it is possible before removing pellets: (*a*) to withdraw the added sodium chloride therapy; (*b*) to provide a diet or low sodium chloride content; or (*c*) to administer added potassium medication (20–40 cc. daily of a 10% solution of potassium citrate).

COMPLICATIONS IN THE COURSE OF DESOXYCORTICOSTERONE TREATMENT

1. In rare instances patients may react unfavorably

[2] *Technic of pellet implantation.* The infrascapular region posteriorly is a convenient site for implanting pellets. Observation of strict asepsis is imperative. The operative field is prepared with iodine and alcohol and the site of the incision is infiltrated with procaine 1:200 solution. A transverse incision 3–7 cm. in length is made a few centimeters below the inferior spine of the scapula. With blunt dissection a number (corresponding to the number of pellets) of small pockets, 3–4 cm. in depth, are prepared in the subcutaneous fat. The opening of each pocket in the subcutaneous fat is held far enough apart by a nasal dialator to permit pellets to gravitate to the bottom of the pocket without the use of force. This is very important for if the opening is too small the pellet may be crushed by the force used to insert it. The wound is closed with subcuticular sutures of fine black silk. It is possible to insert as many as 10–15 pellets through a single incision.

to the sesame oil in which the crystalline hormone is dissolved. This untoward reaction is usually characterized by localized redness, pain and tenderness at the site of the injection associated with constitutional symptoms (fever and malaise) (12). It is possible to avoid further reactions by substituting a different type of oil or by implanting, subcutaneously, pellets of crystalline hormone.

2. Excessive edema may result from an overdosage of hormone (2,21). This complication is most likely to be observed within the first two or three weeks of treatment when the maintenance dose of hormone is being established. Edema disappears rapidly following the reduction in the dose of the sodium chloride or synthetic hormone. It is well not to reduce the dose of both sodium chloride and hormone simultaneously as a crisis may be precipitated.

3. Continued treatment with excessive quantities of synthetic hormone and added sodium chloride may result in signs and symptoms of pulmonary edema (21). This complication is most likely to occur in patients with evidence of pre-existing myocardial damage or in patients who are permitted unrestricted activity following the institution of treatment, particularly after a prolonged period of invalidism.

4. Hypertension may be noted after continued sodium chloride and hormone therapy (2). The occurrence of this complication may be prevented by adjusting carefully the dose of hormone and added sodium chloride.

5. Hypoglycemia may occur during the course of acute infections or gastro-intestinal disturbances in which there is either an increased carbohydrate requirement or a decreased intake, in patients treated with desoxycorticosterone acetate alone.

6. It is possible to produce low serum potassium values in patients treated for a prolonged period with excessive doses of sodium chloride and desoxycorticosterone acetate (2). Symptoms of muscular weakness somewhat suggestive of the changes which have been observed in patients with familial periodic paralysis may ensue (28). It is generally agreed that it is undesirable to restrict the potassium intake of patients given sodium chloride and desoxycorticosterone acetate at present. There is some discussion as to whether it may not be desirable to give additional potassium medication to patients treated with desoxycorticosterone acetate (29).

Desoxycorticosterone acetate may be used with safety if care is taken in following the patient closely and in regulating the dose of hormone. Changes in blood pressure, body weight, and circulation should be followed carefully during the course of treatment. Added sodium chloride medication should be given very cautiously in conjunction with desoxycorticosterone acetate treatment.

SUMMARY

A great advance has been made in our knowledge and understanding of the action of the adrenal cortical hormone. In the absence of complications, the life maintenance of patients depends in a great measure upon the restoration of electrolyte balance, plasma volume and blood pressure. However, under conditions of stress, patients may succumb if the abnormality in carbohydrate metabolism is not corrected promptly. Little is known concerning the fundamental nature of the disturbance in pigment metabolism.

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DISCUSSION

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I am very happy to see reported this clinical account of the procedure which Dr. Thorn has so successfully employed in the treatment of patients who have Addison's disease. His therapeutic results have been excellent, and others if they will follow his recommendations undoubtedly will serve their patients well. What I have to add in this discussion is limited to a few items in which entire agreement with Dr. Thorn may be lacking. This is not to be interpreted as disagreement in anything essential. The experience of The Mayo Clinic for the most part fully supports what Dr. Thorn has recommended.

Dr. Thorn's comment on the greater frequency now than formerly of cases of Addison's disease without tuberculosis is borne out by our experience. Reviewing this, Dr. Cragg has reported thirty necropsies. Adrenal tuberculosis existed in 12 of these, in two the lesion was carcinoma, in one it was undetermined and in 15 the adrenals were atrophic without evidence of tuberculosis or other disease.

Referring to work of Ingle[1] which showed that atrophy of the adrenal cortex could be provoked in normal animals by hormone therapy, Dr. Thorn commented that the fact is not likely to be of clinical significance. I fully agree that it represents no reason for withholding substitution therapy in cases of established adrenal cortical insufficiency, and yet I would urge those who resort to very potent adrenal products for treating asthenic conditions which are not clearly adrenal in origin to bear the possibility of danger in mind. The precaution will be imperative I think, if and when the chemists provide a synthetic form of the carbohydrate factor of the adrenal cortex. This factor, represented by Kendall's compound *E*, is much more effective in causing adrenal cortical atrophy than other constituents of adrenal extracts.

The introduction of a diet restricted in potassium for patients who were given little or no substitution therapy, was followed in our hands by definitely improved therapeutic results. This diet, however, is not to be used when patients are receiving desoxycorticosterone. A restricted intake of potassium not only is not needed under such circumstances but actually can be injurious. The synthetic hormone has so powerful a salt and water retaining effect that potassium must be made available or intercellular fluid may increase abnormally and venous pressure may rise dangerously. The fact is clearly revealed by clinical experiments recently reported by Tooke, Power and Kepler.[2] An adequate provision of potassium is accomplished by giving a diet relatively rich in meat.

Likewise, when patients are receiving desoxycorticosterone not only is it unnecessary but also in my opinion and in that of my colleagues it probably is definitely unwise to supplement the salt received in the diet with sodium citrate. On the other hand, when adequate substitution therapy has not been available or has not been used, the security of patients has been increased when sodium citrate as well as extra sodium chloride has been administered. In my opinion the indication for additional sodium ions is not dependent on measurable renal insufficiency. I think that Dr. Thorn's data, as well as ours, reveal that proportionately more sodium than chloride is excreted by the kidneys at all stages of adrenal cortical insufficiency.

When the low potassium diet has been used and adequate amounts of sodium chloride and sodium citrate have been given, we have not been able to observe that the addition of small doses of aqueous extract of adrenal cortex (1 cc. injected two or three times daily) has been of any appreciable advantage.

Treatment with diet plus sodium chloride and sodium citrate (low potassium, high sodium) has been effective in our hands, even in cases that Dr. Thorn would classify in his *Group C*. With greater severity than this or with cases in which complications exist, hormone becomes necessary. Then, however, relatively large doses of aqueous extract of adrenal cortex become necessary (5 or 10 cc. injected two or three times a day). Under such circumstances little or nothing is accomplished with smaller doses.

Disturbing experiences with two patients who had Addisonian crisis, who were treated with desoxycorticosterone in addition to water, salt, glucose and cortical extract,[3] have led us to avoid the use of large doses of the synthetic hormone in this emergency. For years our results in the treatment of crisis have

[1] Ingle, D. J.: The effects of administering large amounts of cortin on the adrenal cortices of normal and hypophysectomized rats. *Am. J. Physiol.* 124: 369–371. (Nov. 1) 1938.

[2] Tooke, T. B., Jr., Power, M. H. and Kepler, E. J.: The tolerance of patients suffering from Addison's disease to potassium while such patients are being treated with desoxycorticosterone acetate. *Proc. Staff Meet., Mayo Clin.* 15: 365–368. (June 5) 1940.

[3] Wilder, R. M.: Progress in treatment of Addison's disease. *Proc. Staff Meet., Mayo Clin.* 15: 273–277. (May 1) 1940.

been excellent, and it seems to us wiser to postpone the administration of desoxycorticosterone until the stage of crisis has been passed, and small doses (2 to 5 mg.) can suffice for the maintenance of normal salt and water balance. Too rigid a rehydration of the dehydrated tissues of the patient in crisis seems to be undesirable.

I am glad Dr. Thorn has stressed the importance of maintaining a continuous supply of glucose, particularly during the treatment of crisis. The danger of hypoglycemia is very real under such circumstances. It must be borne in mind with any case of Addison's disease when the patient is deprived of a regular intake of food. We also are in complete agreement with Dr. Thorn in the matter of resumption of normal activity when patients have lived a life of invalidism for some time before satisfactory treatment has been obtained. The remarkable improvement in strength and in the feeling of well-being which usually follows soon after starting treatment with the new synthetic hormone is likely to encourage patients to place a greater strain on their weakened hearts than can be tolerated.

Our experience with implantation of desoxycorticosterone has been too limited to justify much comment on this procedure. One patient was given an implantation of 508 mg. and remained in excellent condition without other treatment for a period of 6 months. A second implantation of equal size was then administered without disadvantage. A theoretical objection to this method of treatment is the difficulty of determining when the implant should be renewed. I also feel that before attempting implantation it might be wise to maintain the patient on daily injections of hormone in oil for a period longer than the one month recommended by Dr. Thorn. My reason for this is that an occasional individual receiving desoxycorticosterone has done very well for a month, but later there developed hypertension or other evidences of intolerance for the dose of desoxycorticosterone administered. It would be my suggestion that a 6-months' period of subcutaneous administration of desoxycorticosterone in oil precede any implantation.

Not considered by Dr. Thorn is the question of what to do for the patient maintained with desoxycorticosterone if and when infection or trauma intervenes. Patients with Addison's disease are unusually sensitive to insult of any kind, and a complication may be fatal unless, when it occurs, provision is made for the increased requirement for substitution therapy which may accompany it. For the same reason that we do not like to use desoxycorticosterone in the treatment of patients in crisis, we hesitate to increase the dose of desoxycorticosterone to meet possibly increased requirements for hormone that result from complications. Our practice at present is to advise the patient not to change the dose of desoxycorticosterone in emergencies, but rather to supplement this dose with 5 cc. or more of cortical extract given subcutaneously at 8-hour intervals.

We entirely agree with Dr. Thorn's conclusion that desoxycorticosterone properly used represents a great advance in our ability effectively to treat adrenal cortical insufficiency. Our experience, however, indicates that the new drug is a two-edged sword, and unless used wisely may precipitate unnecessary fatalities.

WILLARD O. THOMPSON, M.D.

From the Department of Medicine, Rush Medical College of the University of Chicago and the Presbyterian and Cook County Hospitals, Chicago, Illinois

I have read Dr. Thorn's article on the treatment of Addison's disease with a great deal of interest. In the light of our experience in Chicago there are many points on which we agree and some important points on which there is some difference of opinion. In general, it is fair to say that we have not been as enthusiastic as Dr. Thorn about the efficacy of desoxycorticosterone, although we believe its isolation and synthesis represent important therapeutic advances. The best method of treating patients is still the administration of large doses of adrenal cortical extract (from 10 to 40 cc. daily of the Wilson product). There appear to be some patients who can not be controlled with any dose of desoxycorticosterone acetate. In our hands, the effective dose both of desoxycorticosterone acetate and of cortical extract has been greater than in Dr. Thorn's experience.

We have not obtained any clinical evidence of regeneration of adrenal cortical tissue and believe, as Dr. Thorn does, that stimulation of the gland with pituitary preparations containing the adrenotropic factor may be desirable in some cases but impractical with preparations available at present.

We have found oral administration of adrenal cortex extract to be less than 20 per cent as effective as parenteral administration. Since the material for each

route costs about the same per unit, oral administration is not practical at the present time.

While some patients may be maintained with sodium salts alone for long periods of time, maximum clinical improvement can not be produced in this way and sooner or later all patients require continued hormone therapy.

Dr. Thorn suggests the administration of 2 to 3 cc. of adrenal cortex extract or 1 to 2 mg. of desoxycorticosterone acetate daily in moderately severe cases, and from 4 to 9 cc. of cortical extract, or 2 to 5 mg. of desoxycorticosterone acetate daily in severe cases. He apparently supplements these doses by the administration of sodium salts. In our experience, 2 cc. of cortical extract and from 1 to 2 mg. of desoxycorticosterone acetate daily have produced very little effect and I would be inclined to wonder whether a large part of the improvement might not have been produced by sodium salts. We have previously pointed out that the only real test of the efficacy of substitution treatment is its ability to maintain patients in good condition without any other form of therapy.

The severity and duration of crises vary. We are, therefore, unable to lay down any hard and fast rules for changes in treatment on the various days of the patient's illness. The treatment must be adapted to the individual problem. In some instances a maintenance program may be resumed in 24 hours and in others only after 7 to 10 days. Furthermore, in the treatment of a crisis we use larger doses of cortical extract than Dr. Thorn does and give sodium chloride and dextrose together in the form of 5 per cent dextrose in normal saline. Our treatment of a crisis may be outlined as follows.[1]

1. Administer intravenously 10 cc. or more per hour of an active adrenal cortex extract. There is no danger at present of giving too much. In severe cases it may be necessary to administer as much as 40 cc. per hour for several hours.

2. Administer intravenously about 8.5 gm. of sodium chloride and 50 gm. of dextrose every 6 hours in the form of 5% dextrose in normal saline. Fifty cc. of 2.5% sodium citrate may be added to one liter of fluid in each 24-hour period.

3. Substitute oral administration of sodium salts for intravenous administration as soon as they can be retained.

Early in a crisis the patient may be revived with extract alone, but if nausea and vomiting have supervened, it is usually necessary to administer fluids intravenously as well. When extract alone is sufficient the total dose required usually does not exceed 40 cc. given in divided doses of 10 cc. per hour. If nausea and vomiting are marked no attempt should be made to revive the patient with extract alone but fluid and extract both should be started intravenously at once in the doses outlined.

In the treatment of a crisis the dose of extract is gradually reduced as nausea and vomiting subside and appetite returns. At the same time, the oral administration of sodium salts is substituted for intravenous administration, or their administration discontinued altogether if it is planned to use substitution therapy only. For the purposes of maintenance the following measures may be used.

1. Administration of an active adrenal cortex extract—a minimum of 10 cc. per day of the Wilson product (750 grams of fresh beef adrenal) and not infrequently, 30 cc. or more daily. It may be noted that these doses are much greater than those recommended by Dr. Thorn.

2. Administration of desoxycorticosterone acetate in oil or in pellets (minimum effective dose in oil intramuscularly is 10 mg. per day, in our experience).

3. Addition of sodium salts to the regular diet (12 gm. sodium chloride and 6 gm. sodium citrate daily).

4. Combination of 1 and 3.

5. Combination of 2 and 3.

Maximum improvement can be produced only by using adequate substitution therapy and if adequate doses of extract or desoxycorticosterone acetate are used, it is not necessary to supplement them with sodium salts. In patients receiving sodium salts alone, this form of therapy may be supplemented with the administration of a low potassium diet but in patients receiving large doses of cortical extract this is not necessary, and in patients receiving large doses of desoxycorticosterone acetate, is actually harmful because this material may produce abnormal lowering of the concentration of potassium in serum while maintaining the sodium concentration within normal limits. In both man and the rat its administration may be followed by the development of flaccid paralyses, which in the rat can be controlled by the administration of potassium salts. Other untoward effects of its use are edema of dependent portions of the body, hypertension and sudden death (apparently cardiac in nature). We have had two sudden deaths from its use in patients who could not be maintained in a satisfactory condition. In other patients it has worked surprisingly well. The reasons for the failures are not clear but it is very evident that desoxycorticosterone acetate, while a very interesting and very valuable therapeutic agent, does not represent complete substitution treatment in Addison's disease.[2]

[1] THOMPSON, W. O., P. K. THOMPSON, S. G. TAYLOR, 3rd, AND W. S. HOFFMANN: *Endocrinology* 24: 774. 1939.

[2] THOMPSON, W. O.: *J. Mich. State Med. Soc.* 39: 648. 1940.

R. A. CLEGHORN, M.D.

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Anyone attempting a discussion of a comprehensive paper written by an acknowledged authority on a subject is at a certain disadvantage if his remarks are to be more than an echo. However no one can hope to say everything about so involved a subject as Addison's disease in a few pages and experience with patients may vary in different places: hence, an addendum to even such an accomplished treatise is justified.

Concerning the importance of acid-fast infection in Addison's disease, our observations agree with Dr. Thorn's. Of a series of 30 cases encountered by the writer, active tuberculosis in regions other than the adrenals has unquestionably contributed to the death of four. Clinical or X-ray evidence of tuberculosis of the adrenal or other tissues has been obtained in only seven other cases and in these it was relatively inactive and did not constitute a problem in treatment.

While an increased renal excretion of sodium chloride and water probably occurs with the development of crises in most cases of Addison's disease, it has been found that the marked reduction in plasma volume present in such crises in dogs may be associated with little or no such loss by the kidney.[1] Presumably, a similar condition may be encountered clinically. In any case, it has been our experience, as well as that of others, that severe deterioration in a patient's condition may occur despite apparently adequate control of electrolyte metabolism. Instances of this type have become more common since the introduction of desoxycorticosterone as a therapeutic agent. This does not mean that this drug is noxious but only, as Dr. Thorn has pointed out, that it lacks the carbohydrate regulating factor of the adrenal cortex.

The types of failure or crisis encountered in cases adequately but not over-treated with desoxycorticosterone fall into three categories: (*a*) those developing bouts of hypoglycemia; (*b*) those showing weakness and edema associated with cardiac irregularities; (*c*) those exhibiting weakness, edema and hypotension without cardiac irregularities. Marked improvement in such types of failure, without reducing the dose of desoxycorticosterone, has accompanied supplementary therapy in our experience. For this purpose, small amounts of aqueous cortical extract (2–5 cc., 100–250 gm. adrenal gland) injected daily are often adequate. Despite this increase in salt-retaining hormone, the patient's edema disappears. Similar benefit has been observed to follow the use of Upjohn's 'Cortalex' tablets, 12 to 15 daily, though we have been unable to satisfactorily sustain severe cases on a moderately low salt intake on 'Cortalex' tablets alone. Correction of associated cardiac irregularities—usually multiple ventricular extra systoles—in these cases is more difficult and, in our experience, they respond only after more intensive treatment with aqueous extract.

Recently we have observed edema in a severe case of Addison's disease receiving as little as 1 mg. of desoxycorticosterone daily. No added salt was given but the edema disappeared and the patient felt stronger when given supplementary therapy. No cardiac irregularity was present but the heart was extraordinarily small as is so frequently the case in Addison's disease. In this case we believe the cardiac inadequacy, not uncommon in desoxycorticosterone treated cases, was unusually prominent. What principle is in the supplementary treatment which leads to the patient's improvement in such cases we do not know. We suspect, however, that it is the carbohydrate factor.

The results in 4 of 12 cases which we have treated with desoxycorticosterone over a period of 5 to 22 months may be classified as good.[2] These patients are following their former occupations. In two other cases the results may be classified as fair. They are not working but enjoy considerable, if restricted, activity. Four others require supplementary treatment with other adrenal preparations; they are invalids. One patient has entered a remission and gets along very well without added salt or any hormone therapy except during an infection. One patient has died. These results, which will be published in detail later, represent the degree of success obtainable with desoxycorticosterone in our hands. It is our opinion that further experience will result in more failures to sustain patients rather than in greater success. The necessity of obtaining a supply of carbohydrate factor which might be expected to improve treatment is a chemical problem and will in time, no doubt, be surmounted.

The maximum blood pressure rise following treatment with desoxycorticosterone, as Dr. Thorn has pointed out, may be delayed 4 to 16 weeks. Since restoration of the electrolyte disturbance and plasma

[1] CLARKE, A. P. N., R. A. CLEGHORN, J. K. W. FERGUSON AND J. L. A. FOWLER: *Proc. Roy. Soc. Can.* 1940.

[2] CLEGHORN, R. A.: Can. Med. Assn. Annual Meeting, June, 1940.

volume to normal values occurs in a few days,[3,4] the persistence of hypotension must be dependent on some factor other than the diminished blood volume and abnormal blood chemistry. It seems reasonable, in the light of recently acquired evidence suggesting that cardiac function is deficient in this disease, to implicate the heart as the cause of this persistence of hypotension. It is also suggested that the hypotension characteristic of this disease even during remissions may be dependent on cardiac asthenia rather than on electrolyte or blood volume disturbances.

Detailed comment on the succinctly outlined plan of treatment presented by Dr. Thorn would be redundant. However, it is perhaps not out of place to emphasize the benefit of hypertonic saline in the initial treatment of patients in characteristic crisis. On the basis of both clinical and experimental experience we feel it is exceedingly effective and permits more rapid restoration of depleted salt reservoirs than the use of normal saline. The osmotic property of the solution may also be a factor in the rapid correction of electrolyte disturbances. It is our routine to use a solution of the following composition: 900 cc. normal saline, 700 cc. 6% saline, and 400 cc. 50% glucose. The first 500 cc. is injected rapidly in ½ to ¾ of an hour, with 25 cc. of aqueous extract. Another 700 to 1,500 cc. is given in the next 12 to 18 hours. The intravenous solution is then changed to glucose in normal saline and continued as indicated. Apart from the use of a slightly more hypertonic solution than that recommended by Dr. Thorn, our line of treatment follows substantially the same lines. It perhaps should be added that Addison's disease patients can receive too much fluid parenterally and careful watch should be made that this does not occur.

In concluding this discussion a word on the use of thyroid extract is in order. A few cases of Addison's disease seem to suffer from true hypothyroidism and benefit from the use of thyroid extract.[5] We have encountered four such cases. It should be emphasized that the low basal metabolic rate often encountered in this condition is not usually indicative of true hypothyroidism and that thyroid extract then does harm rather than good. Clinical signs of diminished thyroid activity must be present in addition to a low metabolic rate to justify thyroid therapy. Care must be taken that the patient is receiving adequate adrenal hormone therapy or a crisis may be precipitated.

The elucidation of the physiology of the adrenal cortex as exemplified in the study of Addison's disease, while it has led to more effective therapy, has also opened up new problems and shown that even this malady is a more complicated phenomenon than was suspected earlier.

[3] Thorn, G. W., R. P. Howard and K. Emerson, Jr.: *Jour. Clin. Invest.* 18: 449. 1940.

[4] Ferrebee, J. W., C. Ragan, D. W. Atchley and R. F. Loeb: *J.A.M.A.* 113: 1725. 1939.

[5] Cleghorn, R. A.: *Jour. Clin. Invest.* 17: 526. 1938.

Abstracts of
CURRENT CLINICAL LITERATURE

HANS O. HATERIUS, *Abstract Editor*

ADRENALS

DIJKHUIZEN, R. K., AND E. BEHR.

Adrenal hypertrophy in infants: a new clinical entity of the neonatal period. *Acta Paediat.* 27: 279. 1940.

Four cases of infants are described, 3 of whom (♂ ♂) died with the diagnosis of intestinal stenosis. The 4th child, a ♀, also showed the picture of intestinal stenosis at the beginning of the disease and died with symptoms of a gastro-intestinal stenosis disorder. In 3 cases, autopsy revealed hypertrophy of the adrenals, of which the histological substratum is reported. Postmortem examinations was refused in the 4th case. A few similar cases of adrenal hypertrophy have been recorded in the literature. As a rule these children were also found to have suffered from intestinal disorders. Most of the patients were boys or pseudo-hermaphrodites. It is suggested that an increased cortical hormone activity existed in these cases. Further clinical, pathological and experimental data are required to define and, if possible, to explain the clinical picture.—From *Clinical Abstracts.*

FIROR, W. M.

Treatment of Addison's disease by implantation of synthetic hormone. *Ann. Surg.* 111: 942. 1940.

The daily requirement of desoxycorticosterone acetate was determined in 17 patients, and it was estimated that 0.5 mg. by daily injection corresponded to a tablet of 125 mg. Pellets placed in the 17 patients have met their requirements for periods of 4 to 9 months. Several have had a 2nd implantation, and in 1 apparently a partial regeneration of cortical tissue has occurred. All but 2 have returned to active work, and all have gained weight, with uniform improvement in diastolic and systolic blood pressure. There has been no suggestion of hypertension. Positive Na and Cl balance has been restored, with normal concentrations of K, Na and Cl ions in the plasma. Hematocrit and plasma volume determinations have revealed a persistent normal value. None has lost all pigmentation. There have been no untoward effects.—H. O. H.

GARVIN, C. F., AND H. S. REICHLE.

Death presumably due to the use of the salt restriction test in the diagnosis of Addison's disease. *Ann. Int. Med.* 14: 323. 1940.

A death, presumably caused by the use of the salt restriction test in the diagnosis of Addison's disease, increases the evidence that this test is not without danger.—Author's abstract.

REINSTEIN, H.

Desoxycorticosterone and adrenal cortical extract in the treatment of Addison's disease. *Bull. New York M. Coll., Flower & Fifth Ave. Hosps.* 3: 1. 1940.

Three cases of Addison's disease treated with various commercial preparations of adrenal cortical extract, high Na-low K diet, and high Na intake, responded poorly. One of the patients died in crisis despite such intensive treatment. Two of the patients showed sustained objective and subjective improvement and final stabilization when subsequently treated with desoxycorticosterone.—From author's abstract.

GONADS

ALTENBURGER, E.

Hormonal origin and therapy of prostatic hypertrophy *Endokrinologie* 22: 344. 1940.

Twelve patients were treated by intramuscular injection of 25 mg. testoviron daily for 3 consecutive days. The dose was then reduced to 5 to 10 mg. per day for 3 days in the week. Favorable results in reducing difficulty in micturition due to enlarged prostate, reduction in the amount of residual urine, and in some cases notable reduction in the size of the prostate are claimed.—W. J. Atwell.

AYCOCK, W. L.

A subclinical endocrinopathy as a factor in autarceologic susceptiblity to poliomyelitis. *Endocrinology* 27: 49. 1940.

Two series of experiments are recorded. In the 1st set, the injection of estrogenic substance into castrate immature female monkeys enhanced resistance to intranasal instillation of the virus. The 2nd series comprised a small number of comparative urinary estrogen assays on poliomyelitis patients and normal individuals. The results indicate a higher average excretion of estrogenic substance in the group of poliomyelitis cases. Autarceologic susceptibility to poliomyelitis may lie in some fault in the economy of estrogenic substance.—Author's summary.

BAGBY, B. B.

Urinary prolan excretion during a menstrual cycle. *J. Lab. & Clin. Med.* 25: 687. 1940.

The urinary prolan excretion of a normal woman was determined for 1 month on the 1st morning specimen, using ovarian and uterine weights of immature rats as indicators. Prolan was found on the 15th and 16th days prior to the next menses which is supposed to be the date of ovulation.—Author's abstract.

BISHOP, P. M. F., R. K. BOWES, M. BOYCOTT, R. KELLAR, T. N. MACGREGOR AND B. C. MURLESS.

Estrogenic properties of stilbestrol dipropionate and hexestrol. *Lancet* 1: 629. 1940.

Stilbestrol dipropionate and hexestrol have estrogenic properties similar to those of stilbestrol, so far as they are capable of the following actions: (1) inducing uterine

hemorrhage in cases of amenorrhea; (2) relieving the symptoms of the menopausal syndrome; (3) leading to the appearance of cornified cells in the vaginal smear in menopausal cases; (4) restoring the normal conition of the vulva and vagina in senile atrophic vaginitis; (5) relieving the pain of dysmenorrhea; (6) inhibiting lactation. Toxic effects, while not severe, developed in 21.6% of cases treated with stilbestrol dipropionate and in 4.5% of cases treated with hexestrol—L. B. Shpiner.

BUXTON, C. L.

Pregnandiol determination as aid in clinical diagnosis. *Am. J. Obst. & Gynec.* 40: 202. 1940.

Determinations were made in 4 patients during and following injection of 30 mg. progesterone per dayf ro 3 days. Three had subtotal and 1 a total hysterectomy. Two excreted Na pregnandiol glucuronidate, so the uterus, therefore, was not necessary for the metabolic process involved. Synthesis is believed to occur in the liver. Greatest yield was found in PU, and no pregnant woman has been reported not to excrete pregnandiol. Its absence therefore may be of value in the negative diagnosis of pregnancy. Results of 78 simultaneous pregnandiol determinations and endometrial biopsies in sterility clinic patients made it apparent that pregnandiol is excreted only during time that endometrium is being activated to a secretory phase. Because of a number of variables the quantitative analyses are subject to variation, and quantitative differences cannot be made a basis of diagnosis.—H. O. H.

COHEN, M. R., AND I. F. STEIN.

Laboratory and clinical experience with oral pregneninolone. *Am. J. Obst. & Gynec.* 40: 713. 1940.

Pregneninolone was administered orally in daily amounts of 15 to 30 mg., to a total dosage of 300 mg. per month, to 37 ♀ ♀ complaining of menometrorhagia, dysmenorrhea, premenstrual tension, amenorrhea, and mazoplasia. In 31% mild undesirable side effects appeared, seldom so severe as to necessitate withdrawal of the drug. Treatment proved effective in approximately ½ of 25 patients with menometrorrhagia but proved of little benefit in dysmenorrhea. Tested in rats, the orally active progestational substance was found to cause suppression of gonadotropic activity of the anterior pituitary, as well as definite kidney damage.—Hans O. Haterius.

CONNALLY, H. F., D. I. DANN, J. M. REESE AND L. H. DOUGLASS.

A clinical study of the effects of diethylstilbestrol on puerperal women. *Am. J. Obst. & Gynec.* 40: 445. 1940.

Diethylstilbestrol was administered to 200 puerperal women in an attempt to show effects in postpartum uterus with special reference to endometrial regeneration. Five mg. doses per day were given until, usually, the 10th day, an average amount of 50 mg. No apparent immediate effect on early involution of the puerperal uterus was noted, but at the 21st day pelvic examination demonstrated a more rapid involution than was found in control groups. No toxic side effects were noted. While lactation was suppressed in 70% of cases, complete suppression was not obtained in the dosage used. The routine use of diethylstilbestrol in prophylactic therapy of puerperal endometritis remains to be demonstrated.—From author's summary.

DAVIDOFF, E.

Psychiatric aspects of the treatment of cryptorchidism. *J. Nerv. & Ment. Dis.* 91: 724. 1940.

No definite correlation could be said to exist between descent of the testes, improvement in mental status or personality and change in the constitution. escent of the testicles did not mean necessarily change or improvement in the mental status. The behavior of the patient could not be ascribed to the cryptorchidism alone. There are various conditions in which undescended testicles may occur and there is apparently no psychiatric entity associated with this condition. The occasional improvement in the mental status could not be ascribed to the endocrine therapy alone. When the total picture is evaluated, the restricted clinical value of the hormone therapy becomes more apparent. The pseudocryptorchids should be differentiated from the true cryptorchids. In true cryptorchids descent was noted in only 3 of 13 cases. —Author's abstract.

DAVIS, M. E.

Clinical study of stilbestrol. *Am. J. Obst. & Gynec.* 39: 938. 1940.

Stilbestrol was used in treatment of 100 patients with menopausal symptoms. One mg. at bedtime controlled symptoms. About 20% of those given 5 mg. at first complained of nausea with or without vomiting, and reduction of dosage to 1 mg. obviated the untoward symptoms. Ninety-three of the 100 treated were completely relieved. Sudden cessation of therapy was often followed by vaginal bleeding in 10 to 20 days. Two cases of primary amenorrhea was given 1 mg. by mouth daily, with complete development of secondary sex characters and reproductive organs. The gonads remained dormant, however, and patients remained normal only if treatment was continued. Studies over long periods are required to determine desirability of continuous treatment, and optimal amount to be used remains to be determined.—Author's abstract.

DIDDLE, A. W., AND W. C. KEETEL.

Hematometra and hematocolpos following the administration of stilbestrol. *Am. J. Obst. & Gynec.* 39: 791. 1940.

Among 10 women given 1 to 5 mg. stilbestrol daily, 3 had withdrawal bleeding and annoying nausea and vomiting. Relatively large doses of stilbestrol were administered over a 74-day period to a woman having senile vaginitis. The quantity given failed to bring about complete cornification of the vaginal mucosa, but did lead to uterine bleeding with the production of hematometra and hematocolpos subsequent to spontaneous obliteration of the vagina.—Author's abstract.

DINGEMANSE, ELIZABETH, AND E. LAQUEUR.

The content of male and female hormone in the urine of patients with prostatic hypertrophy. *J. Urol.* 44: 580. 1940.

In 13 of 16 patients with prostatic hypertrophy the amount of urinary comb growth promoting substances was less than 20 I.U. per day. In only 3 cases did the amount of hormone excreted reach 50, 44 and 50 I.U., respectively. The amount of estrogenic substances in the same urines reached 20 I.U. in 1 case only. The ratio of I.U. estrogen to I.U. comb growth promoting substance varied between 0.4 and 2.2. In absence of prostatic hypertrophy the urine of 16 men above 50 years of age was examined and in only 4 cases was less than 18 I.U. of comb growth promoting substance per 24-hour sample. In 3 cases the amount of estrogen was less than 40 I.U. while in 9 cases it exceeded 100 I.U. The average amount excreted in 16 cases was 98 I.U. per 24 hours. In this group the ratio was 2 or over in 15 cases. Three cases of carcinoma of the prostate did not show an increased content of sex hormone.—From authors' summary.

EISENSTADT, J. S., M. APPEL AND M. FRAENKEL.

The effect of hormones on the undescended testis. *J.A.M.A.* 115: 200. 1940.

The importance is emphasized of clinical differentiation of abnormally situated testes which will descend when they approach adult size and weight from the group of true undescended and ectopic testes. Gonadotropic substances may be harmful, in larger doses, to testes which have not reached the scrotum. At operation, 7 cases showed marked evidence of degeneration after use of chorionic gonadotropic hormone. Rats rendered unilaterally cryptorchid on the 30th day of life were given, with suitable controls, 50 R.U. of chorionic gonadotropin weekly for 4 weeks. The cryptorchid testes, both treated and untreated, showed atrophy, thickening of the capsule, edema and cellular infiltration and marked atrophic changes in the seminiferous tubules. The changes were more marked in treated animals. According to the authors gonadotropic substances have no value in the preoperative care of true undescended and ectopic testes, which always require operative treatment for their correction.—D. J. Stephens.

ERVING, H. W., C. SEARS AND J. ROCK.

Clinical experiences with equine gonadotropic hormone. *Am. J. Obst. & Gynec.* 40: 695. 1940.

In a series of 48 cases and under a variety of dosages the equine gonadotropic hormone was not shown to stimulate ovulation in women with anovulatory bleeding or amenorrhea, nor did it have apparent effect in cases of sterility. Three cases of cysts of the ovary were noted following therapy. Exhaustive clinical experimentation is necessary before the value of the hormone will be established.—From authors' summary.

FRASER, I.

Precocious puberty. *Brit. J. Surg.* 27: 521. 1940.

This is a report of a case of extreme verilism in a boy of 12 months, presumably the youngest on record. Precocity in bone and dentition was noted. The value of the capon and colorimetric tests, as well as the ponceau fuchsine stain, was demonstrated. Until the age of 6 months he was an average child, when the penis began to enlarge rapidly, the prostate became the size of a walnut and erections were almost constant. Masturbation took place frequently, pubic hair appeared and acne on the face appeared. The face became old for his age, the voice deep pitched, hands greatly enlarged and muscular development excessive, the appearance of the epiphyses was greatly in advance of his age and body weight increased out of all proportions. He ate about three times the supply of food usually given. Mentally he was retarded. He was unable to talk and rarely used the "mamma-baba" words expected of a child of one year. He seemed to have little affection except for food. From the age of 6 months he lost his cleanly habits as regards urine and feces. He became bad tempered and difficult to manage. The author does not clain that these had any direct connection with his increased virilism. Briefly the boy's age was: by calender, 12 months; by mental advancement, 12 months; by bone epiphyses, 5 years; by dentition, 3 years; by sexual organs (penis and prostate but not testicles) 18 years. Biologic tests carried out on the urine revealed that the child at 12 months of age was more virile than the average adult male. Abdominal exploration revealed a tumor the size of a golf ball above the right kidney. The rest of the abdominal contents seemed healthy. After a considerable delay the second operation was performed when the boy was 18 months old. A high kidney incision was made. The twelfth rib was extracted and the adrenal tumor delivered with much greater ease and less bleeding than was expected. The tumor was pyriform, with the apex apparently attached without a stem to the inferior vena cava. Twenty hours later, he collapsed and died. A complete necropsy was performed but no anomalies other than enlargement of the vesicles and prostate could be observed.—*Abstract, J. Nerv. & Ment. Dis.*

FURUHJELM, M.

Excretion of estrogenic and androgenic substances in the urine of women. *Acta Obst. et Gynec. Scandinav.* 20: Suppl. 1: 1. 1940.

Excretion of estrogenic and androgenic substances was determined in 2-day lots of urine from 14 healthy ♀ ♀ for at least 1 ovarian cycle and similarly for 10 cases of myoma of the uterus on samples collected for 2 weeks prior to and 2 weeks after operation, if any. Androgenic substances, determined spectrophotometrically. Curves representing excretion in normal ♀ ♀ showed estrogen excretion with 1 or, occasionally, 2 pronounced peaks, with a marked decrease during menstruation. Activity of 2-day samples varied between 20 I.U. and 400 I.U. of estrone. In 11 of 14 cases no decrease in androgen excretion occurred at the menses. There was a distinct tendency to parallelism between excretion of androgen and estrogen during the intermenstruum. Similar conditions were found in 10 cases of uterine myoma. In 2 castrates no estrogen could be demonstrated in the urine up to 2 weeks postoperatively. Androgenic substances were present in the same amount as before and in approximately

same amounts as in normal women.—From author's summary.

GLASS, S. J., H. A. EDMONDSON AND S. N. SOLL.

Sex hormone changes associated with liver disease. *Endocrinology* 27: 749. 1940.

Urinary bioassays of 8 males hospitalized for cirrhosis of the liver revealed low androgen values and a high titer of free estrogen. Gynecomastia and testis atrophy were present in the majority of cases. The data are taken to indicate a failure of the cirrhotic liver to inactivate estrogen.—From authors' summary.

GEIST, S. H., J. A. GAINES AND U. J. SALMON.

Inhibitory action of testosterone propionate on the human ovary. *Proc. Soc. Exper. Biol. & Med.* 44: 319. 1940.

Two women were treated with 925 and 1225 mg. testosterone propionate, respectively. Vaginal smears, vaginal biopsies and endometrial biopsies were performed before and after the hormonal administration. The ovaries were removed at the end of the period of treatment and examined histologically. Testosterone propionate inhibited follicle formation, ovulation and corpus luteum formation, this being associated with regressive changes in the endometrium and vaginal mucosa. This action of testosterone propionate is evidently mediated through inhibition of the gonadotropic activity of the hypophysis.—U. J. Salmon.

GREENHILL, J. P., AND S. C. FREED.

Further studies on the androgen therapy of gynecologic disorders. *Am. J. Obst. & Gynec.* 39: 636. 1940.

In confirmation of observations made elsewhere, testosterone propionate inhibited ovarian activity, resulting in suppression of uterine bleeding and involution of the genitalia, and in regression of fibromyomas. The changes persisted only so long as androgenic treatment was continued. Despite positive evidence of beneficial effects of androgen therapy in ovarian disorders, caution is urged in the use of testosterone propionate because of the demonstrated virilism induced in some patients receiving large doses. Moreover, weight gain and occasional acneform eruptions may occur, changes which regress upon cessation of treatment. A follow-up some 7 to 12 months after treatment revealed that more than 50% continued to derive appreciable benefit after discontinuing therapy. Patients with dysmenorrhea tended to relapse more often than those with excessive uterine bleeding, but the series of patients was too small to permit of more definite conclusions.—From authors' abstract.

HADLEY, H. G.

Anterior pituitary test for early pregnancy. *Am. J. Obst. & Gynec.* 39: 894. 1940.

The results of 50 tests definitely showed that the local reaction to the intradermal injection of two minims of APL hormone is unsatisfactory as a test for pregnancy.—Author's abstract.

HAMBLEN, E. C., J. M. ARENA AND W. K. CUYLER.

Hand-Schüller-Christian disease. Report of a case in which urinary androgens were titrated. *Am. J. Dis. Child.* 60: 352. 1940.

The excretion of androgens in urine of a 29-month-old white ♂ with Hand-Schüller-Christian disease was approximately 10 times normal. This was related to the general disturbance of lipoid metabolism, rather than to an excessive activity of the gonads or adrenal cortex. No. Na pregnandiol glucuronidate was excreted.—H.O.H.

HAMBLEN, E. C., W. K. CUYLER, AND MARGARET BAPTIST.

Urinary androgens and uterine bleeding. *Endocrinology* 27: 16. 1940.

The average urinary titers of androgens of 9 ♀ ♀ were determined by the colorimetric technic of Oesting during bleeding and nonbleeding phases. Seven of the 9 showed significant decreases in these titers during bleeding. The average daily titer of the entire group during the nonbleeding phase was 72 I.U. and for the bleeding phase 50 I.U.—Authors' summary.

HAMBLEN, E. C., W. K. CUYLER, AND D. V. HIRST.

Studies of urinary excretion of progestin. I. Following intramuscular injections of progesterone. *Endocrinology* 27: 33. 1940.

Two young ♀ ♀, who were receiving daily intramusc. injs. of 20 mg. of progesterone, excreted no biologically active progestin in a total of 3 complete 24-hr. specimens of urine studied by the bioassay method of Corner and Allen. During periods of therapy where in the 2 patients received 90 mg. and 200 mg. of progesterone respectively, total urinary excretions of Na pregnandiol glucuronide were 3 mg. and 5.4 mg.—Authors' summary.

HAMBLEN, E. C., W. K. CUYLER, AND D. V. HIRST.

Studies of urinary excretion of progestin. II. Following oral administration of pregnen-in-on-3-ol-17 (Anhydro-hydroxy-progesterone). *Endocrinology* 27: 35. 1940.

A young ♀, who was receiving daily by mouth 40 mg. of pregnen-in-on-3-ol-17 (anhydro-hydroxy-progesterone) excreted no biologically active progestin in the urine during 2 24-hr. periods, investigated by the bioassay method of Corner and Allen. During the entire period of therapy, in which a total of 320 mg. of this sterol was given, no Na pregnandiol glucuronide appeared in the urine and no alterations occurred in the urinary titers of androgens.—Authors' summary.

HAMBLEN, E. C., C. J. PATTEE AND W. K. CUYLER.

Alterations of urinary excretion of androgens by estrogenic therapy. *Endocrinology* 27: 734. 1940.

The androgenic titers of 22 females with various grades of ovarian failure were quantitated by Oesting's method prior to and during oral and injectional therapy with estrogens. The % of decrease during therapy of these moderately elevated titers were 26, 30, and 14 for the 3 groups of patients studied. Orally administered estrogens, although given in smaller quantities than injected estrogens, were equally effective in altering androgenic values.—From authors' summary.